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THE ENDOCRINE ORGANS

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THE ENDOCRINE ORGANS

THE ENDOCRINE ORGANS

AN INTRODUCTION TO THE STUDY OF
INTERNAL SECRETION

BY

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SECOND EDITION

WITH NUMEROUS ILLUSTRATIONS

PART I

THE THYROID, THE PARATHYROIDS, AND THE
SUPRARENAL CAPSULES

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PREFACE TO THE SECOND EDITION

THIS book was originally founded upon a course of lectures (Lane Medical Lectures) delivered at Stanford University, California, in the summer of 1913. The lectures were issued in the following year amongst the publications of the University, but in an abbreviated form and without illustrations. It also happened that the proofs, which had been sent for correction, failed to reach me; so that the work as it appeared contained an unusual number of incidental errors. On these and other grounds I judged it desirable, with the concurrence of the University authorities, to publish the substance of the lectures in a revised form, with the addition of the tracings and photographs which were used to illustrate them: thus both enabling the subject to be treated more fully and affording the opportunity of presenting it to a wider audience. The book so constituted was published in 1916, and the issue was sold out within three years. I have not found time until now to prepare another edition, but the work has been available in a translation into French by MM. Guy Laroche and G. Richard; to this a considerable amount of new matter was added both by the translators and myself. These additions have also been embodied in a Spanish translation by Professor J. M. Bellido; it appears therefore that the demand for the work was widespread. It has accordingly been thought desirable now to issue a new English edition embodying the extensive additions to our knowledge which have appeared since the first publication. The result is the production of what is to all intents and purposes a new book, which differs from the original one not only in containing a far greater amount of material in the text, but also by the circumstance that the sources of the more important or recent facts are indicated in footnotes. It is hoped that this may render the work useful to those engaged in research, although for a complete bibliography the student of endocrinology would naturally consult Biedl's well-known work, *Innere Sekretion*, of which nearly five hundred pages are occupied by the titles of papers dealing with this subject, or *Endocrinology and Metabolism* (1922), edited by L. F. Barker, of which more than seven hundred pages are devoted to a similar enumeration.

EDINBURGH,
January 1924.

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THE ENDOCRINE ORGANS

AN INTRODUCTION TO THE STUDY OF INTERNAL SECRETION

CHAPTER I

GENERAL CONSIDERATIONS

INTERNAL SECRETIONS AND THE ORGANS WHICH FURNISH THEM

MATERIAL which is passed into the blood or lymph from any tissue or organ of the body forms its *internal secretion*, and organs which are believed to possess the function of passing such material into the blood or lymph are termed *internally secreting* or *endocrine organs*.¹ This expression is not usually extended to organs like the lymph-glands, of which the material production is of a purely morphological character, although until recently all such organs used to be included along with the true endocrine glands, the functions of which were at that time unknown, in the general expression of *ductless glands*. Under this last term were comprised not only the organs to which we now commonly ascribe internally secreting functions, such as the thyroid, parathyroids, the suprarenal capsules or adrenals, the pituitary body or hypophysis cerebri, and the pineal gland or epiphysis cerebri, but also the thymus gland, the tonsils, lymph-glands and lymph-follicles, and the spleen: with these the bone-marrow is associated. But the proof of the existence of internally secreting functions in connexion with the organs in the last category is so inferior to that which we possess regarding the thyroid, parathyroids, suprarenals, pituitary, and even the pineal, that we must exclude them from the class of bodies which secrete specific chemical substances into the blood for the purpose of influencing other organs. It is to the latter class that I intend to restrict my remarks, and it is to them and them alone that the term “endocrine” will be applied in these pages.

The thymus, tonsils, lymph-glands, and spleen are all lymphoid structures and obviously mainly if not entirely concerned with the production—perhaps also in the case of the spleen and lymph-glands with the destruction—of the morphological constituents of the blood. There is no evidence that can be relied upon

¹ From *ἐνδον*, within, and *κρίνω*, to separate. The term “endocrinology” is now in common use to denote the study of the internal secretions.

that they discharge specific materials into the circulation which affect other organs, although various observers have obtained from extracts prepared from them effects indicating that such extracts contain substances which either cause contraction, or produce relaxation if contracted, of the plain muscle of the blood-vessels, intestine, uterus, etc.¹ These effects resemble those of certain bodies such as histamine and choline, which have been found in greater or less quantity in many tissues and organs, and their presence cannot be regarded as sufficient reason for ascribing to those which yield them an internally secreting function. Moreover, surgical removal of the glands in question gives negative results—which is not the case with any of the true endocrine organs. Until lately the thymus was generally regarded as belonging to the last-named class of bodies by virtue of the fact that various observers had described changes in metabolism (especially affecting bone formation) and alterations in the generative organs (especially increased rate of growth and development) as a result of its removal. But the careful experiments of Park and M'Clure² have shown that no appreciable result is obtained by removal of this organ, and the evidence for an endocrine function is therefore no greater than that for any other of the lymphoid structures enumerated. On these grounds, although the thymus was included amongst the endocrine organs in the last edition of this work, it has been omitted from the present edition.

It follows from what has been said that by the expression *endocrine organ* we imply an organ which is known to form some specific chemical substance within its cells, and to pass this directly or indirectly into the blood-stream. The substance thus formed is the active material of the secretion, just as ptyalin is the active agent of the salivary secretion. But while in the case of such glands as the salivary their secretion is led by a duct to the exterior, in the case of the endocrine glands the secreted material remains within the body and passes into the blood: hence the term *internal* applied to their secretions.

It must be clearly understood that although this passage of a specific substance into the blood is an essential part of the doctrine of internal secretion, the definite proof of such substances in the blood has only been furnished in very few cases. Nevertheless there is little reason to doubt their passage into the blood in all cases. For it is not probable that active specific substances would be formed in special glands unless for the performance of specific functions, and to reach other structures they must pass into the blood. Yet even if we inject quite a considerable amount of so potent a material as adrenaline into a blood-vessel in a living animal, after a very short time it can no longer be detected in the blood. Far less can we expect to find the small amount which is habitually secreted into that fluid. But concerning the manner of disappearance of this and other products of the internally secreting organs we are ignorant.

¹ Vincent and Sheen, *Journ. Physiol.*, xxix., 1903; Stern and Rothlin, *Journ. de physiol.*, xviii., 1919; and J. L. and E. M. Miller, *Journ. Physiol.*, xliii., 1911.

² *Amer. Journ. Dis. Children*, xviii., 1919 (dogs). See also Hammar, *Arch. f. d. ges. Physiol.*, cx., 1905, and Pappenheimer, *Journ. Exper. Med.*, xx., 1914.

The expression *internal secretion* was originally employed by Claude Bernard to describe the sugar which, as he showed, is passed from the liver-cells into the blood. It has also been used to designate all materials which are contributed to the blood by the tissues. In this sense carbon dioxide and other products of metabolism which are taken up by the blood in its passage through the capillaries, or are received by it through the medium of the lymph-stream, are internal secretions, and every tissue is an internally secreting structure. It is, however, convenient to restrict the term to secretions containing specific organic substances such as the active chemical agents which are produced by certain ductless glands, and this is the sense in which the expression will be employed in this book (see also pp. 5-8).¹

The production of specific chemical agents which are passed into the blood and carried by it to influence distant structures is not confined to the ductless glands—an active internal secretion may be produced by other organs than these. A notable example is met with in the pancreas, the more obvious function of which is the production and secretion into the intestine of pancreatic juice; which, by virtue of the ferments it contains, is the most active agent in the digestion of foodstuffs within the alimentary canal. It was shown, however, by v. Mering and Minkowski² that the pancreas possesses an internal secretory function which is of even greater importance in the economy than its long-recognised external secretory activity. For by totally removing the pancreas in animals, these observers proved that the presence of the gland, and of some substance yielded by it to the blood, is essential to the proper utilisation of carbohydrate material by the tissues, so that when the pancreas is totally removed carbohydrate is no longer stored in the liver and muscles and utilized by the organism, but is converted into glucose, and accumulates in the blood, where it produces hyperglycæmia and whence it is removed by the kidneys, producing glycosuria.

Now it is known that the pancreas possesses, besides the secreting alveoli which form the enlarged and blind terminations of its ducts, a special kind of secreting cells which are massed together into islets of irregular shape and variable number and size, having a special kind of blood-supply. These islets, which were first described as a distinct element of pancreatic tissue by Langerhans,³ have been originally developed from and may retain a connexion with the ducts of the organ, in this respect resembling the ordinary alveoli. But in the course of growth they have lost all open connexion with the ducts; their cells have acquired specific properties; and their function is without doubt different from the ordinary cells of the gland. With considerable probability the special internal secreting function above mentioned has been ascribed to them, and in support of this it may be stated that in many if not most cases of diabetes these cells are found to have undergone degeneration.

¹ The term *incretion* has been recently introduced as a short expression to denote *internal secretion*, but is scarcely a happy one.

² *Centrbl. f. inn. Med.*, 1889, and *Arch. f. exp. Path. u. Pharm.*, xxvi., 1890.

³ *Diss.*, Berlin, 1869.

They, in fact, form an organ within an organ, and collectively may be regarded as belonging to the group of internally secreting or endocrine glands. It may be added that our present knowledge of the causation of diabetes, as well as the most hopeful method of treating it, are based mainly on these observations.

An example of a tissue devoted to the formation of both an external and an internal secretion is found in the epithelium which lines the duodenum. The functions of this epithelium which have been longest known are those of promoting the absorption of digested food materials and of helping to furnish the secretion known as the intestinal juice. But it was discovered by Bayliss and Starling¹ that if an extract of the duodenal epithelium is boiled with dilute hydrochloric acid and, after neutralisation, is injected into the blood-stream of an animal, a rapid flow of pancreatic juice is determined. It had already been known that the gush of acid gastric juice through the pylorus, or the painting of the mucous membrane of the duodenum with dilute acid, would determine a flow of pancreatic juice, but this flow had been supposed to be brought about as a reflex act by excitation of a local nervous mechanism by the acid. The observations of Bayliss and Starling rendered it clear, however, that this is not the correct explanation of the phenomenon; but that the flow must rather be regarded as due to the absorption of some internal secretion into the blood: the material of this internal secretion being produced in an inactive form by the epithelium-cells, and becoming so altered by the dilute acid as to be converted into an agent which, after absorption into the blood-stream, excites the secreting cells of the pancreas to activity.

To the active substance which is yielded by the epithelium-cells of the duodenal mucosa the name *secretine* was given by Bayliss and Starling, whilst they termed *pro-secretine* the inactive material contained within the cells before the action of dilute acid upon them. The active material is obviously of the nature of an internal secretion; it appears, however, not to be produced by a special structure, certainly not by a special organ, but, so far as one can tell, by the ordinary cells which line the mucosa and extend into its glands.

A yet more remarkable example of the coincidence of external and internal secretory functions in the same organ is supplied by the generative glands (ovary and testicle). It has been known from time immemorial—the experiment is repeated daily for commercial purposes in thousands of animals, and was long practised upon man for domestic reasons in Oriental countries—that the removal of the generative glands in the young male usually entirely prevents the development of the accessory generative organs, such as the prostate, and of the features which characterise the male sex externally. These changes have been prevented by successfully grafting testicular substance into the castrated animal.

Again, removal of the ovaries in the young female exerts a profound influence over the organism, and prevents the development of many female character-

¹ *Journ. Physiol.*, xxviii., 1902.

istics. In some cases, even in the adult, removal or atrophy of the ovaries has been noticed to lead to the development of male characters. Instances of this have been often recorded in birds. In young mammals removal of the ovaries is followed by arrest of development of the uterus. These changes may be prevented by successfully transplanting the ovaries, or by grafting an ovary from another animal of the same species into the peritoneum or elsewhere. It seems likely, therefore, that the result of removal is due in both male and female to the absence of an internal secretion of the generative gland.

THE NATURE OF THE ACTIVE PRINCIPLES CONTAINED IN THE INTERNAL SECRETIONS

We have compared the active materials of the internal secretions, which are formed within cells and passed out into the blood, to the active agents of the ordinary secretions, which are directed on the exterior by means of a duct. But the comparison cannot be pressed. In the case of the external secretions, the active agents when present are always of the nature of ferments. They belong to the class of bodies known as *enzymes*. The conditions and modes of action of these bodies are for the most part familiar to the biologist. They occur not only in secretions, but in the bioplasm of most, if not of all, cells; indeed the chemical activity of the cell appears to depend on its contained enzymes. Although far simpler in chemical nature than the bioplasm by which they are produced, and in no sense endowed with life, enzymes are very probably of a protein nature, and are readily destroyed by heat in presence of water. The active materials of the endocrine organs, on the other hand, are for the most part not rendered inactive even by prolonged boiling, and are certainly of a much simpler chemical constitution than enzymes. They are dialysable; and although most of them have not yet been isolated in a crystalline form, due probably to the fact that it is difficult to obtain them free from impurities, some of them have been so obtained, and at least one—the active material of the adrenal medulla—has been prepared synthetically. Many of them act instantly: their action, as Starling has pointed out, being similar to that produced by the active principles of drugs, especially those of organic, *i.e.* of vegetable, origin. These also operate by immediate chemical action, being conveyed to the parts which they influence in solution in the circulating blood. But while some of the materials of the internal secretions produce their effects upon the tissues immediately, others operate more slowly, so that the results of their action may only become apparent after a prolonged period of time. The latter class usually exert their influence upon the growth and nutrition of special organs or of the body generally; they are accordingly termed by Gley *morphogenetic*.¹ One at least, that yielded by the thyroid, has a marked effect on metabolism in general, and through this upon various functions of the body. The secretions of other endocrine organs have been

¹ He suggests the name *harmozones* for them (ἁρμόζω, I govern).

reported to exert a similar influence, but in some cases they may be regarded as acting through the thyroid.¹

None of the substances we are dealing with are known to cause the production of antibodies when introduced into "foreign" blood. Their action is similar in all animals, however different from the animal yielding the secretion.

As with drugs, some of the principles yielded by the endocrine organs act by stimulating or exciting cell-functions: this is notably the case with the principle obtained by the action of acid on the duodenal epithelium which, when injected into the blood-vessels, increases the secretion of pancreatic juice. Others depress or inhibit those functions: an example of this is met with in extract of placenta, which when injected into the blood-vessels tends to prevent the secretion of milk. To stimulating principles such as that contained in the extract of duodenum after treatment with acids the term *hormone* (from ὀρμάω, I stir up) was originally applied by Starling,² and the expression has been extended to include the active principles of all internal secretions. So long as only exciting agents were known, there could be no objection to the extension of this term, but since agents which produce depression or cessation of function have been shown also to be produced in the body—and their number will probably become considerable as the nature of the internal secretions is more fully examined—it is advisable to employ an expression which will discriminate between these and the stimulating agents. On this account we distinguish the action of the depressants from that of the excitants by the use of the term *chalone* (χαλάω, I make slack). A *chalone* may therefore be defined as an endocrine product which inhibits or diminishes activity, as distinguished from a *hormone*, which excites to increased activity.³

Starling does not, however, confine the use of the term *hormone* to organic principles of an endocrine nature. His definition is much wider. "By the term *hormone*," he says, "I understand any substance normally produced in the cells of some part of the body and carried by the blood-stream to distant parts, which it affects for the good of the organism as a whole" (*Proc. Roy. Soc. Med.*, vol. vii., 1914, Therap. and Pharm. Sect., p. 29). He then proceeds to give as examples of hormones, secretine, adrenaline, and carbonic acid—the last, which is produced by the tissues in general and more especially by muscular tissue, stimulating the respiratory centre to activity. Obviously this definition would include many substances normally present in the blood, such as water, urea, glucose, and inorganic salts, which are produced in various parts of the body and affect distant organs such as the kidneys: indeed it

¹ J. C. Aub and M. Taylor, *Endocrinology*, vi., 1922, where also the literature of the subject will be found. For an interesting speculation by Keith on the possible dependence of racial characteristics on the relative development of the several endocrine organs, see the *Lancet*, ii., 1919.

² *Verhandl. d. Naturforscher-Versammlung*, Stuttgart, 1906.

³ The original expression employed by Bayliss and Starling (*Journ. Physiol.*, xxviii., 1902) in their paper on secretine was *chemical messenger*. This is more appropriate as a general term than *hormone*, because it includes all chemical agents which produce an effect at a distance, whether such an effect be excitatory or inhibitory.

may be supposed that most circulating materials will, when we know more about their history, come into the definition. The expression *hormone* has not hitherto been employed by physiologists and clinicians in this extended sense; the term has usually been restricted to the active organic principles of the internal secretions. But it is best to employ the term *hormone* in the sense in which it was used by its inventor, *i.e.* to denote any substance in the blood which excites cells of the body to activity, and to express by a more general term those specific substances which are produced by the organs of internal secretion for the purpose *either* of exciting *or* of restraining the activity of other organs. Since the most characteristic feature of the action of these substances is the resemblance to the action of drugs, such as the vegetable alkaloids, I have suggested¹ employing for these specific substances the general title *autacoid substances*, or, simply, *autacoids* (*αὐτός*, self, and *ἄκος*, a medicinal agent or remedy).² An autacoid may accordingly be defined as a specific organic substance formed by the cells of one organ and passed from them into the circulating fluid to produce effects upon other organs similar to those produced by drugs. Such effects are either in the direction of excitation, in which case the endocrine substances producing them are *excitatory autacoids* and would come under the expression *hormones*, or in the direction of restraint or inhibition, in which case they are *restraining* or *inhibiting autacoids* and would be classed as *chalones*.³ The action of an autacoid may therefore be described as *hormonic* or *chaloneic*, according to the kind of effect it produces.

A characteristic example of chaloneic or restraining action is furnished by the internal secretion of the ovaries (see p. 5). If these are removed there is manifested a tendency on the part of the female to develop male characteristics. Thus a hen deprived of ovary shows the secondary sexual characters of the cock of the same breed: the whole body becomes bigger, the tail feathers grow, the crest and spurs enlarge, and from its external appearance the animal would unquestionably be taken for a cock. Moreover, the change is not purely morphological, but is accompanied by physiological alterations characteristic of the male bird. The spayed hen flaps her wings, crows like a cock, and even attempts to "tread" other hens. If an ovary or even part of an ovary be now successfully transplanted into such an animal, the chaloneic or restraining influences of its internal secretion again operate, the male characteristics disappear, and the ordinary hen characters are resumed (Crew).

Some autacoid substances appear to produce opposite results in different parts. Thus the adrenaline of the suprarenal medulla in solutions of a certain strength causes contraction of the plain muscle of the blood-vessels and inhibition of that of the intestines. But in both cases the action may be regarded as that of a hormone or exciting agent, for both effects are produced by stimulation of the end substance or excitable substance produced in cells under

¹ *Proc. 17th Internat. Med. Congress*, London, 1913.

² Already in general use in the form *panacea*, a universal remedy.

³ This seems to be better than the expressions suggested by Biedl of *exciting hormones* and *inhibiting hormones*, since the former expression is a tautology and the latter a contradiction in terms.

the influence of the sympathetic nerves. Nevertheless the possibility of the same autacoid substance acting under some circumstances as a hormone or excitant, and under other circumstances as a chalone or depressant, must be borne in mind. This, indeed, serves to illustrate the drug-like nature of these principles, for such inversion of action under difference of circumstance is known to occur with some drugs.

METHODS OF DETERMINING THE FUNCTIONS OF ENDOCRINE ORGANS

Two general methods are employed for this purpose, the one being the observation of the changes which result from partial or complete surgical removal of the organ in man and animals, or its destruction by disease; the other, observation of the changes which result from the administration of the organ itself or of extracts prepared from it, or the effects of an outpouring of its secretion caused by stimulation of its nerves, or the results of implantation, of overgrowth, or of overfunctioning.

DEPRIVATION OR DIMINUTION OF FUNCTION PRODUCED BY SURGICAL OPERATION, OR BY DISEASE, OR BY INJURY

The effects of surgical removal, of arterial ligature, and of disease or injury are in many cases striking, and are of much assistance in arriving at conclusions regarding the endocrine functions of internally secreting organs. We shall see that this is the case with the thyroid and parathyroids, the suprarenal capsules, the pituitary body, the pancreas, and the organs of generation.

EFFECTS OF SURGICAL IMPLANTATION OR GRAFTING OR OVERGROWTH

The results of surgical grafting or implantation are usually less easy to obtain on account of the difficulty experienced in getting such grafts to take.¹ This is indeed only possible when obtained from a closely related animal. But when this difficulty has been overcome the results are of value in arriving at conclusions regarding the nature of the internal secretions of an organ. This has been already referred to in connexion with the ovary, and is also illustrated by similar experiments on other endocrine organs, such as the testicle, the thyroid, and parathyroids. Even more striking results are obtained as the result of pathological hypertrophy, which is often accompanied by the outpouring of excessive secretion; one of the most remarkable instances of this being the effects produced when the anterior lobe of the pituitary body becomes enlarged: the enlargement is accompanied by an excessive growth of the skeleton and of other tissues and organs of the body. It must be borne in mind that an excess of secretion may occur, from nervous or other influences, without any obvious hypertrophy of the organ: but in either case the secretion may not possess all the characters of the normal secretion.

¹ See, on the subject of grafts, W. S. Halsted, *Journ. Exper. Med.*, xi., 1909; C. Hesselberg, *ibid.*, xxi., 1915.

EFFECTS OF ADMINISTRATION OF JUICES AND OF EXTRACTS OF THE
ENDOCRINE ORGANS

To test the physiological effects of an organ which is believed to produce autacoids, either the organ itself in the fresh or dried condition, or its expressed juice, or extracts made from it by decoction with water or saline solution may be administered in various ways and the results noted.

In testing extracts of organs for the presence of autacoids, certain precautions must be observed in order to exclude the possible action of nucleo-proteins and other complex organic bodies which might indirectly affect the result. The most important is to use only boiled and filtered extracts—the separation of proteins being if necessary assisted by the addition of chloride of sodium and acetic acid. The amount of fresh material used must be weighed, and the extract made up to a known strength with water or Ringer's solution. Such an extract can be used at once; or if kept in a sterilised condition and over ice may be available for a few days, and in hermetically sealed glass receptacles for a much longer time. But to obtain comparative results it is best to dry the freshly divided glandular substance completely over the water bath and to keep the dried residue in an exsiccator. Extracts can then be made from it with water or Ringer's solution at any time—in some cases it will keep apparently unchanged for years. Ether and alcohol extracts can also be obtained from the dry material, and after evaporating off these solvents extracts of their residue can again be taken up by Ringer and appropriately tested.

As with drugs, the extracts can be administered by the mouth, rectum, or lungs, or by subcutaneous, intramuscular, intraserosous, or intravascular injection. Isolated organs and tissues may be perfused with or immersed in the extract the action of which is to be examined. The intravascular (intravenous) method was first employed by Oliver and myself in 1894 to investigate the physiological action of such extracts, and led immediately to the discovery of the active principles of the suprarenal capsules and of the pituitary body.

Administration by the Mouth and Alimentary Canal: Enteral Administration.—This is well known to be effective in the case of the thyroid, and the fact is taken advantage of in cases of hypothyroidism such as occurs in endemic goitre, cretinism, and myxedema. On the other hand, thyroid juice or the substance of the gland given too freely with the food in normal individuals produces symptoms which have been interpreted as due to excess of the thyroid autacoids in the blood. With smaller doses effects are produced upon metabolism, including an increase of N-elimination, of O_2 intake and of CO_2 output, with reduction of body-fat. Buccal administration of pituitary extracts or pituitary gland substance is stated to yield beneficial results in cases of deficiency of pituitary secretion, although in normal individuals no effect may be apparent. Similarly, buccal administration of suprarenal gives little result in normal individuals, but both in Addison's disease and in certain other affections beneficial effects have been recorded.

Administration by Subcutaneous, Intramuscular, or Intraserosous Injection:

Parenteral Administration.—As with drugs, the effects of administering animal autacoids by hypodermic injection are usually more rapid and more marked than with buccal administration, although in some cases the difference is not striking. But Melzer and Auer have shown that if extracts of the medulla of the suprarenals, or of the posterior lobe of the pituitary body, are administered by intramuscular injection—absorption being promoted by gentle massage—they rapidly cause their characteristic effects. Probably the reason why these extracts when given by hypodermic injection sometimes produce little general result—although the local effects (*e.g.* in causing vasoconstriction) may be very marked—is that the autacoid is rapidly destroyed or in some way packed away in the body; so that when absorbed slowly it is got rid of before any excess is able to accumulate in the blood. This applies only to moderate doses and to the immediate effects. Secondary effects may be seen with large doses; these may be of a striking character.

Intravascular Injection.—The immediate effects—if any—of the animal autacoids are, as with drugs, unfailingly exhibited as the result of the injection into a vein or artery of the extracts containing them. In this manner can be shown the action of extract of thyroid, and of many other organs, in causing a marked but evanescent depression of the blood-pressure: the various effects of extract of suprarenal medulla; such as contraction of blood-vessels with raising of blood-pressure, acceleration of pulse, sometimes preceded or followed by retardation, flow of saliva, erection of hairs, dilatation of pupil, retraction of third eyelid, and protrusion of eyeball, contraction of uterus, vas deferens, and seminal vesicles, inhibition of gastric and intestinal movements and of the bladder: as well as those produced by extracts of the posterior lobe of the pituitary, such as contraction of the blood-vessels with slowing of the heart, increase of secretion from the kidneys, outflow of milk from the mammary gland, contraction of the uterus, of the intestines, and of plain muscle in general.

A caution must be entered against the too hasty conclusion that a particular effect obtained in injecting an organ extract is a specific effect due to an autacoid substance. Especially is this warning necessary in experiments in which the blood-pressure is employed as the gauge of activity. For there are few organs which yield extracts that are absolutely inert when tested by intravenous injection. This applies to many glandular and lymphatic structures, most extracts of which cause a rapid fall of blood-pressure, usually speedily recovered from. The depressor effect is not dependent upon the presence of nucleo-proteins in the extract, as was at one time supposed; but seems to be caused by organic materials of a specific nature varying in different organs, the extracts producing in each case a specific form of blood-pressure curve.¹ Such a material has never been isolated or examined chemically, although often spoken of as *vasodilatin*.² There is reason

¹ Fawcett, Rabe, Hackett, Rogers and Beebe, *Amer. Journ. Physiol.*, xxxvii. and xxxix., 1915.

² Popielski and Panek, *Arch. f. d. ges. Physiol.*, cxxviii., 1909.

to believe that in some cases the active substance in tissue extracts may be *histamine*,¹ and in other cases *choline*.

Extracts of animal tissues—if unboiled—are liable to produce intravascular clotting when injected into the blood-vessels. If this is general, instant death is the result; if localised, it may manifest itself by serious interference with the functions of the nervous system or of other organs: the result of such injection might erroneously be set down to a specific action of the extract injected, although it would only represent the result of an accident. A similar caution applies, although in a minor degree and for a different reason, to effects which may be obtained as the result of buccal and hypodermic administration of animal extracts. Such effects may (unless they are otherwise proved to be specific) be produced by variations in amount of such organic substances as nucleo-proteins, which, when added to the ordinary diet of animals, are capable of affecting growth and metabolism.

It is perfectly legitimate criticism regarding the employment of extracts of organs, that we are not justified in assuming that because we obtain evidence of the presence of active substances in such extracts they are necessarily pre-formed in the organ, and still less that they are passed out from it into the blood.² In fact, as we have seen, actual chemical evidence of the presence of such substances in the circulatory fluids is almost entirely lacking. Nevertheless, the action of extracts of certain of the ductless glands is quite specific, which is not the case with extracts of other organs; and since the active principles contained in such extracts are always readily soluble in water and diffusible, it is difficult not to believe that they are formed with the object of producing their specific action after being passed into the blood, in greater or less quantity according to the needs of the organism. The criticism that with many such extracts an amount of material may be necessary to produce a visible effect which is altogether out of proportion to the size of the endocrine organ the action of which is being studied, loses force if we remember that these organs are extraordinarily vascular and probably proportionately active, so that within a short time a larger amount of active substance may be formed and passed into the blood than is present at any given moment in the cells of the organ. Nor need the action, under physiological circumstances, be so striking as we endeavour to obtain it under conditions of experiment; indeed it is not improbable that in many cases the functions of the internal secretions under normal circumstances are rather facilitating than self-acting.

ACTION ON ISOLATED TISSUES AND ORGANS

One of the most delicate tests for the activity of animal extracts is their effect on isolated plain muscle suspended in Ringer's solution—especially on that of the blood-vessels, uterus, and intestine. Some such extracts, such as thyroid, stimulate the intestinal muscle and inhibit the muscular coat of the blood-vessels, whilst the suprarenal autacoid (adrenaline) usually causes inhibition of intestinal muscle and contraction of vascular muscle; the plain muscle of other organs (uterus, bladder, iris, etc.) being variously affected by

¹ J. J. Abel (with S. Kubota and D. I. Macht), *Journ. Pharm. and Exper. Therap.*, xiii. and xiv., 1919.

² See on this subject E. Gley, *Les sécrétions internes*, 1914.

it. Other tissues and organs which can be subjected to the action of extracts are skeletal muscle and nerve, cardiac muscle, the white corpuscles of the blood, ciliated cells and pigment cells (both within the body and in excised portions of tissue).

TADPOLE TEST

A test which is frequently employed to detect the presence of certain autacoids formed by the endocrine organs—especially those of the thyroid and pituitary—is the feeding of tadpoles with the glands or their extracts. It is found that certain of these organs promote metamorphosis and check growth, whilst others check metamorphosis and promote growth in the larvæ to which they are administered.¹

The terms *substitution therapy*, *organotherapy*, *opotherapy*, *hormonotherapy*, and *autotherapy* have been employed to denote the effects produced by administration of organs and their extracts—especially of the endocrine organs—either with the view of combating symptoms which are believed to be caused by a deficiency in the blood of the autacoids which are produced by these organs, or for the purpose of obtaining a particular pharmacodynamic effect. The fact that such extracts have come into extensive therapeutic use emphasises the essentially drug-like action of the active substances they contain.²

THE INFLUENCE OF ENDOCRINE ORGANS UPON ONE ANOTHER

By no means the least important part of the subject of endocrinology is that which relates to the influence exerted by the secretion of the endocrine organs upon one another. Our knowledge regarding this is still in many respects confused: although the fact that there is such influence is well established for some of the more important of those organs. This influence may take the form either of increasing or of diminishing activity, *i.e.* it may be either *hormonic* or *chaloneic*: and it may act by the secretion of one endocrine gland either influencing the growth and development of another or causing an increase of its secretion, or rendering the tissues upon which it exercises its action more or less sensitive. Special reference will be made in the case of each endocrine organ to such possible correlation with other internally secreting structures.³

GROUPINGS OF THE CHIEF ENDOCRINE GLANDS

Most of the purely endocrine glands can be grouped under the three main heads of *thyro-parathyroid apparatus*, *suprarenals*, and *pituitary*. It is noteworthy with regard to these groups that each of the organs forming the group

¹ Gudernatsch, *Zentrbl. f. Physiol.*, xxvi., 1912.

² This subject is dealt with at some length by J. T. Halsey in *Endocrinology and Metabolism*, 1922.

³ For a summary of the literature of this subject up to that date, see R. G. Hoskins in *Amer. Journ. Med. Sci.*, cxli., 1911.

is compounded of two distinct but usually closely associated parts. Thus the thyro-parathyroid group is composed of thyroid proper and parathyroids ; the suprarenal of cortical and medullary portions ; the pituitary of epithelial and epithelio-neural parts. And in each case the functions of the two portions, so far as is known, appear to be in no way similar, difficult as it is to believe that tissues so closely connected anatomically should have no sort of functional connexion. The close anatomical connexion is, however, sometimes absent, as with those parathyroids which are altogether detached from the thyroid, and as with the paired bodies and the interrenal body of elasmobranch fishes. A close anatomical relationship without any apparent functional bearing is, however, not without examples in other organs ; *e.g.* in the frog there exists a very intimate anatomical connexion of the suprarenal with the kidney, although there is no particular reason to believe that any special functional relationship obtains between the two.

It is further noticeable that in each of the above groups one of the two parts has a more evident, and in a sense more active, function than the other. Thus the removal of the parathyroids occasions symptoms which are far more acute than those produced by the corresponding operation on the thyroid. And extracts of the medullary substance of the adrenals and of the posterior (epithelio-neural) part of the pituitary have an immediate and striking effect on various tissues and organs when injected into the blood-vessels, whilst similar extracts of the cortical substance of the adrenals or of the anterior or epithelial part of the pituitary are without any immediate action. There is, however, in the case of the thyroid and anterior lobe of the pituitary, direct experimental as well as clinical evidence, and, in the case of the cortex of the suprarenal capsules, the testimony of much clinical observation, to furnish reason for the belief that the parts of these glands which at first sight appear less active may exercise, if a slower, yet a no less potent influence upon the organism than the portions the activity of which can be more immediately demonstrated.

CHAPTER II

THE THYROID

DEVELOPMENT AND STRUCTURE

THE thyro-parathyroid group of endocrine glands consists (1) of the thyroid

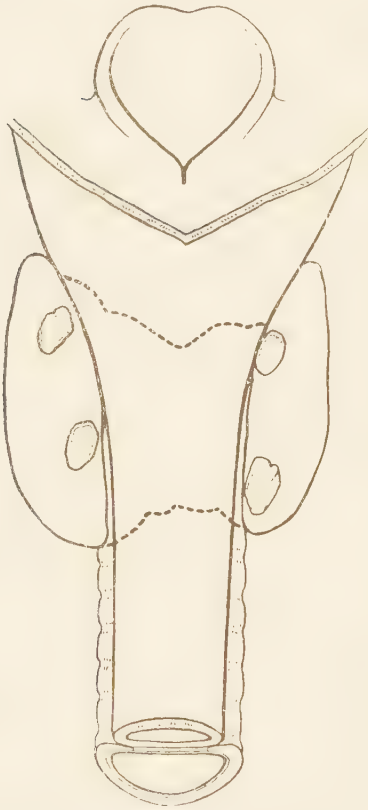


FIG. 1.—Sketch of a preparation of human larynx, trachea, and œsophagus from the dorsal aspect, showing the usual position of thyroid and parathyroids.

proper, a yellowish-red organ with a fibrous capsule, which generally takes the form of two lobes situated on either side of the larynx and windpipe, united by an isthmus over the trachea (fig. 1); (2) of the parathyroids: generally two on each side—one, the upper (parathyroid IV), being usually in contact with the corresponding lobe of the thyroid near its upper and dorsal aspect, whilst the other, the lower (parathyroid III), lies in contact with the corresponding lobe of the thyroid near its lower and mesial aspect, but may be removed a greater or less distance from it, sometimes as low down as the thymus. There is a good deal of variation in their position relatively to the thyroid and to one another.¹ In many animals (dog, cat, rabbit, monkey²) the upper parathyroid is deeply embedded in the substance of the thyroid (but never in man, according to W. G. MacCallum), and it has on that account been termed the “internal” parathyroid, the lower being designated “external.” The expressions parathyroid III and parathyroid IV, which indicate the visceral pouch which gives origin to each gland (see fig. 2), are on the whole the least ambiguous and ought to be employed.

¹ Halsted and Evans, *Annals of Surgery*, xlv., 1907. For variations in the position of the parathyroids in man, see Geis, *ibid.*, xlvii., 1908, and Pool and Falk, *ibid.*, lxiii., 1916. For variations in laboratory animals, see Swale Vincent, *Internal Secretion and the Ductless Glands*, 2nd edition, 1922.

² In the monkey Vincent and Jolly, *Journ. Physiol.*, xxxii., 1904, found the parathyroids usually all embedded in the thyroid.

The thýroid appears very early in the course of development, being nearly the first organ to become distinct in the human embryo. It is seen at about three weeks (embryo of 1.38 mm. long) as a hollow median thickening of the entoderm lining the floor of the pharynx at the level of the interval between the first and second branchial pouches. By the time the embryo is 6 mm. in length the connexion with the cavity of the pharynx is already closed—although it occasionally persists for a time in the form of a duct communicating with the pharynx close to the root of the tongue and known as the *ductus thyreoglossus*. (The original opening is marked throughout life by the *foramen cœcum*.) The single outgrowth may remain simple or may bifurcate. It eventually becomes detached from its connexion with the pharynx and moves into the position of the future thyroid. Cavities become formed within the solid cell mass, giving it a reticular appearance. These cavities are not the permanent vesicles, but serve to divide the mass into a reticular system of flattened epithelial plates, which become fenestrated. Primary follicles are formed in these plates; and, later, from these, the permanent vesicles, by budding or constriction. Colloid does not make its appearance in them until after birth.¹ The evolutionary histology of the thyroid shows it to have been originally developed from the endostyle organ which occurs in Tunicata and in Amphioxus, which opens by a groove into the pharynx. In Ammocœtes the groove is converted into a duct. In all higher vertebrates the duct disappears. In mammals the developing thyroid is joined by the so-called post-branchial

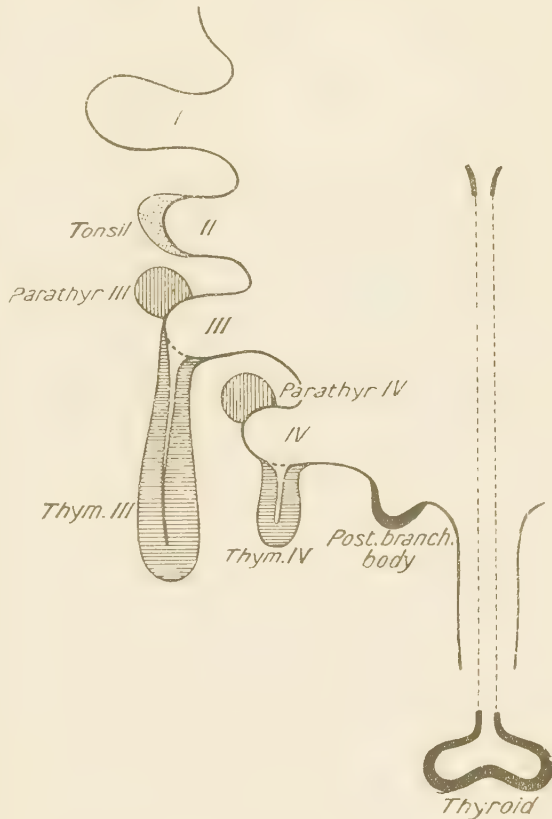


FIG. 2.—Diagram to illustrate the origin of the branchial cleft organs (thyroid, parathyroids, thymus, etc.) in the mammalian embryo.

I, II, III, IV, branchial clefts or pouches; *Parathyr. iii*, origin of lower or external parathyroid from cephalic aspect of third pouch; *Parathyr. iv*, origin of upper or internal parathyroid from cephalic aspect of fourth pouch; *Thym. iii, iv*, origin of thymus from caudal aspect of third and fourth pouches (*Thym. iv* usually forms the part associated with the thyroid); *Post. branch. body*, post-branchial body, which forms a separate organ in lower vertebrates, but in mammals either disappears or is incorporated with the thyroid.

¹ E. H. Norris, *Amer. Journ. Anat.*, xx, 1916. See also on the development of the thyroid, O. Grosser, *Keiber-Mall Handb. der Entwicklungsgesch.*, 1911; F. Livini, *Arch. ital. di anat. e di embriol.*, xviii, 1922.

bodies from the fifth pair of branchial pouches (fig. 2), but these undergo atrophy and form no part of the adult gland.¹

The thyroid may contain a portion of tissue resembling thymus gland, with lymphocytes and corpuscles of Hassall. Such portion of thymus tissue is developed (fig. 2) from the same branchial pouch (thym. IV) as that which gives origin to the upper parathyroid, whereas the main thymus is developed from the third pouch (thym. III), which also gives origin to the lower parathyroid.

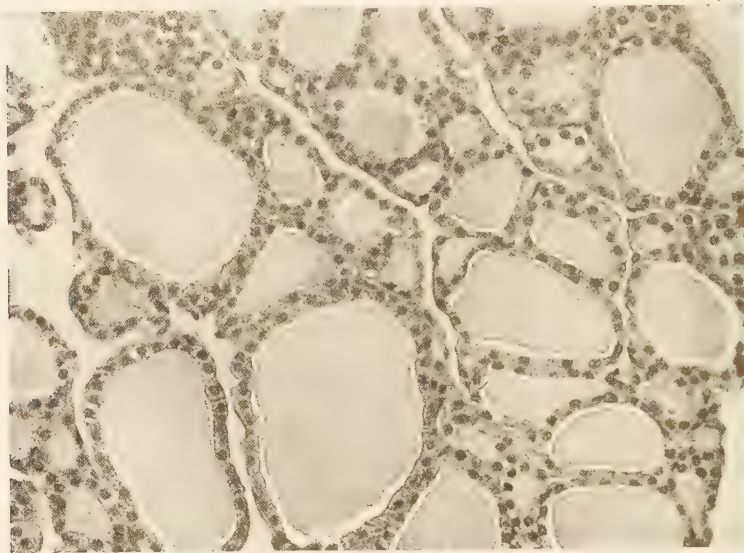


FIG. 3.—Section of thyroid (cat). Magnified 300 diameters. Photograph.

Accessory thyroids, usually quite small, occasionally occur along the remains of the thyroglossal tract and in the deep tissues of the neck and anterior mediastinum; they are sometimes embedded in the thymus. Accessory parathyroids also occur; they are common in the rabbit, and are in this animal often found embedded in the thymus. This is also sometimes the case with the dog, cat, sheep, ox, and goat.²

In the pig, mole, hedgehog, seal, rat, mouse, and guinea-pig only the parathyroids III are ordinarily present, and vary greatly in position relatively to the thyroid. In Ruminants parathyroid III is attached to the apex of the thymus, which extends far forward.

The thyroid is represented in all vertebrates. In *Amphioxus* and *Ammocœtes* it retains an open connexion with the pharynx. Parathyroids have not been found below *Amphibia*.

¹ D. Marine, *Physiol. Rev.*, ii., 1922. The literature of the subject is given in this article.

² R. P. Rossi, *Riv. path. nerv.*, xiv., 1909, and *Clin. vet.*, xxxiii., 1910; D. Marine, *Journ. Exper. Med.*, xix., 1914; Noël Paton and L. Findlay, *Quart. Journ. Exper. Physiol.* x., 1916; Harvier and Morel, *C. r. soc. biol.*, lxvi., 1909; A. Pepere, *Arch. ital. de biol.*, xlix., 1908.

The weight of the whole thyroid in man is from 20 to 25 grams;¹ the average length of each lobe 5–6 cm., breadth 3 cm., and thickness 2 cm. But it may be much smaller or much larger, even in individuals apparently normal.² It is larger in the female than in the male, and much larger relatively in infants than in adults. About 75 per cent. consists of water; the dry residue yields 3·86 per cent. of ash.

Structure of Thyroid.—The thyroid consists of small closed vesicles (fig. 3) of varying shape, but for the most part irregularly spheroidal. The largest are about 0·1 mm. in diameter, but many are much smaller than this. Only in cases of endemic goitre are they much larger. Each vesicle is lined by epithelium, the cells of which are columnar, cubical, or flattened in accordance with the state of distention of the vesicles. There is no definite basement membrane separating the epithelium from the connective tissue and blood-vessels. The vesicles are generally filled by the so-called *colloid*, a viscid fluid in the fresh organ, which is coagulated into a solid substance by fixative reagents. The inter-vesicular substance is areolar tissue, containing in parts many small cells. Some of these are lymphocytes, which may be accumulated in considerable masses, whilst others are like the epithelium of the vesicles, although the identity has not been established. They have sometimes been supposed to be of parathyroid nature, but this is certainly not the case.³



FIG. 4.—Human thyroid and parathyroids from dorsal aspect, showing their arterial supply. (Halsted and Evans.)

The thyroid is one of the most vascular organs in the body; it receives in proportion to its size nearly four times as much blood as the kidneys.⁴ Its average blood-flow (in the dog) is given as 3·5 c.c. per gram per minute: its average oxygen consumption 0·0927 c.c. per gram per minute.⁵ The arteries

¹ S. Mackenzie, *Med. Chir. Trans.*, lxxvii., 1884; Marine and Lenhart, *Arch. intern. Med.*, vii., 1911.

² J. Symington gives the ordinary weight as 30–40 grams (*Queen's Anatomy*, "Splanchnology," p. 320, 1917). For variations in form, see C. F. Marshall, *Journ. Anat.*, xxix., 1895.

³ For different types of structure in animals, see M. Heidenhain, *Anat. Anz.*, liv., 1921. For a somewhat different account of the structure in man, see Williamson and Pearse, *Journ. Path. Bact.*, xxvi., 1923.

⁴ Burton-Opitz and Edwards, *Amer. Journ. Physiol.*, xliii., 1917.

⁵ Knowlton, Dooley, and Curtis, *Amer. Journ. Physiol.*, lix., 1922.

(*inferior thyroid* from the subclavian through the thyroid axis, and *superior thyroid* from the external carotid) form anastomoses at the surface of the organ

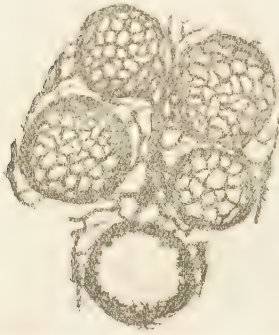


FIG. 5.—Thyroid of dog injected.
low power. Photograph.

but not in its interior.¹ There is, however, a well-marked anastomotic vessel connecting the inferior and superior vessels on the dorso-mesial aspect (fig. 4). The capillaries form a close network around each vesicle, giving a characteristic appearance to an injected specimen (fig. 5): they come into immediate contact with the vesicular epithelium (fig. 6). Each of the parathyroids receives a special arterial branch (fig. 4). There are numerous lymphatics within the organ, and "colloid" like that of the vesicles is occasionally seen within them.² The lymph is conveyed away from the gland on each side by two large efferent vessels which accompany the veins. The gland receives nerves from the sympathetic both directly and through the superior



FIG. 6.—Section of thyroid, human, injected. (Major.) Highly magnified. The close relation of the capillaries to the vesicles is shown.

and inferior laryngeal; they are distributed both to the blood-vessels and to the secreting epithelium.

¹ R. H. Major, *Amer. Journ. Anat.*, ix., 1909.

² But Carlson and Woelfel were unable to obtain physiological evidence (aceto-nitrile test, see p. 54) of the presence of thyroid secretion or of iodine in the lymph from the dog's thyroid, even when the gland was enlarged (*Amer. Journ. Physiol.*, xxvi., 1910).

The vesicles of the thyroid do not always present the appearances above described. Sometimes they are smaller or irregular, with projections into the cavities, and the lining epithelium pronouncedly columnar. In these circumstances the vesicles show little or none of the typical "colloid" contents—although the appearance of the cells is suggestive of secretory activity. It may be inferred that the secreted material in these cases finds a ready exit from the vesicles, and thus fails to accumulate within them; it is possible that it may also be different in quality. So far as can be ascertained, these differences of appearance are seen in animals which are otherwise normal. A glandular structure of this type, but more pronounced, is noticeable in the thyroid in cases of exophthalmic goitre in man. It is usually there interpreted to indicate the production of excess of secretion (hyperthyroidism). A similar structural appearance is

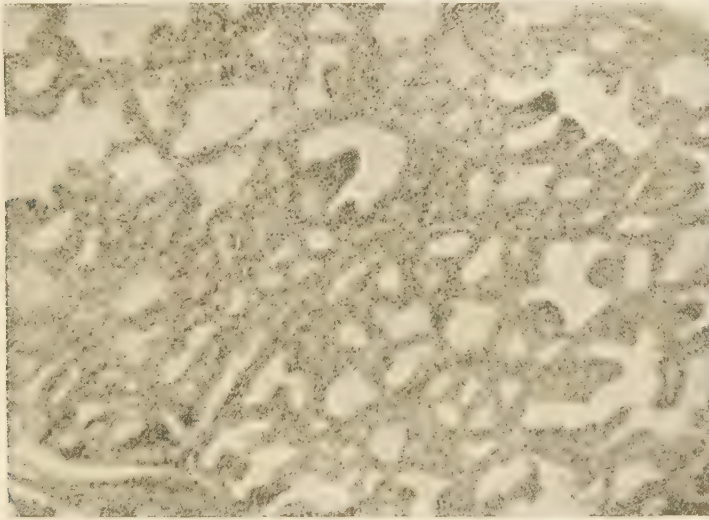


FIG. 7.—Section of a "thyroid remainder" of the dog, the greater part of the gland having been removed by operation 63 days before the animal was killed. Photograph. $\times 80$. (M. Kojima.)

Notice the irregular shape of the vesicles and their variability in size, as well as the large number of cells between them. The colloid is thin and is stained only faintly with hæmatoxylin.

acquired by the "remainder" of the gland after the greater part has been removed (fig. 7). Under these circumstances also we may assume that what has been left is more active than the normal gland.¹

The epithelium-cells of the vesicles contain fatty granules which are said to increase in number with age; they are most numerous near the free border. The colloid is insoluble in alcohol, water, or ether; when coagulated it is readily stained by eosin, less easily by hæmatoxylin. In fixed sections it often appears shrunken away from the epithelium. It is said to be formed from globules which are produced within the cells, and which become dis-

¹ Cf. L. Loeb, *Journ. Med. Res.*, xli., 1920, who also deals with the effects of iodine on the remainder.

charged into the vesicles.¹ It contains the active principles of the secretion, probably forming a store whence they can be extracted as required by the organism. Feeding with iodine compounds increases the amount of colloid.

C. A. Mills² found exposure to warmth to increase the amount of stored colloid; exposure to cold to have the opposite effect.

Two types of cell have been described, *granular* and *colloid*, but these may be variant conditions of the same kind of cell.³ Each cell contains numerous mitochondria and a well-marked reticular apparatus of Golgi. This usually lies between the nucleus and the free surface, but is sometimes seen between the nucleus and the base of the cell.⁴ Bensley⁵ considers this indicates that the

secretion in such cells is formed in the basal part of the cell and is passed outwards directly towards the blood-stream.

Cowdry⁶ finds that in the dog-fish each vesicular cell is furnished with a flagellum, which extends into the colloid filling the vesicle.

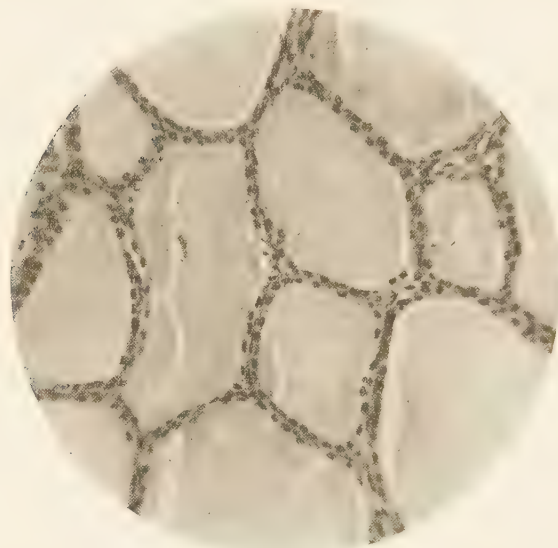


FIG. 8.—Section of thyroid of wild rat. Magnified 250 diameters. The vesicles are seen to be distended with colloid and the cells flattened. (Chalmers Watson.)

The cells of the thyroid are said to be very sensitive to X-rays, which cause them to undergo degenerative changes⁷ and diminish the activity of the gland. Such treatment appears to yield success in some cases of exophthalmic goitre (see p. 52).

A close relationship exists between the size and structure of the thyroid and the state of general nutrition of the animal. The effect of variations of diet upon the thyroid has been studied in rats by Chalmers Watson,⁸ who has shown that all transitions from an active or superactive organ with columnar epithelium and without any great accumulation of colloid in the vesicles, to a gland with flattened epithelium and vesicles greatly distended by colloid, are exhibited under the influence of different diets: the former conditions being in the white rat, typically seen when the animals have been fed upon a

¹ E. Uhlenhuth (in *Ambyostoma*), *Proc. Soc. Exper. Biol.*, xx., 1923.

² *Proc. Amer. Physiol. Soc.*, in *Amer. Journ. Physiol.*, xlv., 1918.

³ O. Langendorff, *Arch. f. Physiol.*, Suppl., 1889.

⁴ Cowdry, *Amer. Journ. Anat.*, xix., 1916.

⁵ *Ibid.*

⁶ *Anat. Record*, 1921.

⁷ Coulaud, *C. r. soc. biol.*, lxxxvii., 1922.

⁸ *Quart. Journ. Exper. Physiol.*, v., 1912.

mixed food such as bread and milk ; the latter when the diet has been composed of lean meat or liver.¹ Prolonged feeding of rats with lean meat leads eventually to a shrinking in size of the vesicles and of the whole organ, these changes being associated with dryness of skin, falling off of hair, and other evidences of hypothyroidism : in carnivora results of this kind were not observed. Reid Hunt² found that as tested with aceto-nitrile (see p. 54) mice produce more thyroid secretion when fed with oatmeal than with most other kinds of food.

Both these conditions of the thyroid, viz. vesicles distended with colloid and with flattened epithelium (fig. 8), and vesicles empty of colloid and with columnar epithelium (fig. 9), were found by Chalmers Watson in wild rats, killed immediately after capture and apparently in complete health.³

Administration of large doses of thyroid substance, as well as of potassium and sodium iodides, causes accumulation of colloid in the vesicles of the thyroid of rats, the epithelial cells becoming flattened.⁴

The effects of vitamins have been studied by McCarrison.⁵ Vitamin-poor diets cause decrease in size and weight of thyroid : vitamin-rich diets having the opposite effect.

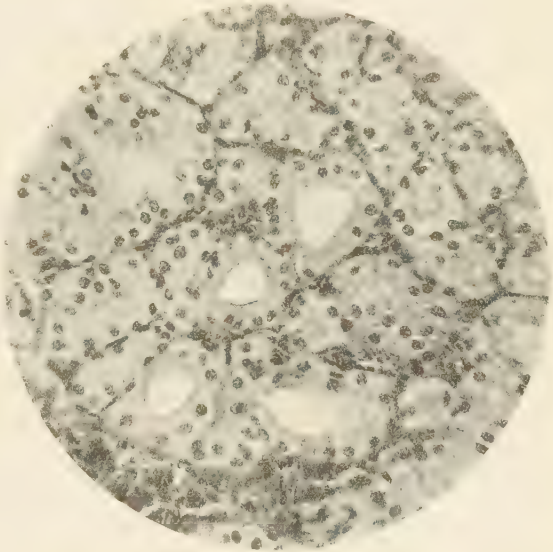


FIG. 9.—Section of thyroid of another wild rat. Magnified 250 diameters. The vesicles contain little or no colloid ; the epithelial cells are columnar. (Chalmers Watson.)

¹ L. M. Degener has obtained confirmatory results (*Amer. Journ. Physiol.*, lx., 1922. See also Tsuji, *Act. Schol. Med. Univ. Imp.*, Kyoto, 1922). A diet containing a large proportion of fat is still more effective in producing enlargement of the vesicles. E. and M. Mellanby, *Proc. Physiol. Soc.*, in *Journ. Physiol.*, lv., 1921.

² *Journ. Amer. Med. Assoc.*, lvii., 1911.

³ For variations of structure in disease of the gland, see Marine, "The Pathological Anatomy of the Thyroid," in *Endocrinology and Metabolism*, ed. by L. F. Barker, 1922. For variations in the thyroid (rabbit) with age, see P. Häggström, *Upsala Läkaref. Förhandl.*, xxi., 1915. In this animal there is a central canal in each lateral lobe, occupied by colloid, and lined by cubical epithelium.

⁴ A. Dingwall Fordyce, *Edin. Med. Journ.*, ix., 1912 ; M. Kojima, *Quart. Journ. Exper. Physiol.*, xi., 1917. The cells of the parathyroids also undergo enlargement under thyroid administration.

⁵ *Indian Journ. Med. Res.*, 1920.

CHAPTER III

THE THYROID (*continued*)

NATURE OF THE AUTACOIDS PRODUCED BY THE THYROID

THE active principle of the thyroid which is concerned with metabolism is usually assumed to be represented by the non-proteid nitrogenous material known as *iodo-thyrin*, or by the compound of this with nucleo-protein (*iodo-thyroglobulin*).¹ The former was prepared from thyroid by E. Baumann,² and found by him to contain a marked amount of iodine (0.3 to 0.9 per mille of dry substance). Iodine appears to be an essential part of the active principle.³ Cameron, who examined the thyroids of numerous species of vertebrate animals for their iodine content, never failed to find evidence of its presence, although the amount was sometimes very small. According to E. Zunz⁴ the human thyroid gland contains on an average 15.53 mg. of iodine (about 0.46 to 0.84 mg. per gram of fresh gland). The thyroid is the only organ in the body which contains iodine in appreciable amount or which is capable of storing iodine. The percentage of iodine in the normal animal seems to be about the same in the two lobes. If the nerves to one lobe only are stimulated, a diminution in the iodine content becomes manifest.⁵

In endemic goitre the enlarged thyroid contains proportionately less iodine.⁶

Marine (working with Feiss and Rogoff)⁷ found that iodine administered as I or KI is at once taken up by the thyroid—even if perfused through the isolated

¹ Oswald, *Zeitschr. f. physiol. Chem.*, xxiii., 1897; xxvii., 1899; xxxii., 1901; *Arch. f. exper. Path. u. Pharm.*, lx., 1909, and lxiii., 1910.

² *Zeitschr. f. physiol. Chem.*, xxi. and xxii., 1895, 1896; *Munch. med. Wochenschr.*, 1896. For other attempts to isolate the active principle, see R. Hutchison, *Journ. Physiol.*, xx., 1896, xxiii., 1898, and *Practitioner*, 1901; Romeis, *Bioch. Zeitschr.*, cxxxii., 1922, and *Arch. f. Entwicklungsmech.*, l., 1922 (abstract in *Endocrinology*, May 1923); also Kendall (results referred to later). For the general chemistry of the thyroid, the article by A. T. Cameron in *Endocrinology and Metabolism* (*op. cit.*) may be consulted.

³ Marine, *Arch. int. Med.*, i., 1908; iii., 1909.

⁴ *Soc. Belge de biol.*, 1919; *Arch. intern. de physiol.*, xvi., 1921. For the iodine content of the thyroid at different ages, see Pellegrini, *Arch. ital. de biol.*, lxx., 1916. There is very little in the foetal thyroid and comparatively little during the first few months after birth.

⁵ Rahe, Rogers, Fawcett, and Beebe, *Amer. Journ. Physiol.*, xxxiv., 1914.

⁶ For the relation of iodine to the structure of the gland and the amount of colloid in its vesicles, see further D. Marine and C. H. Lenhart, *Arch. intern. Med.*, iii. and iv., 1909; and Wilson and Kendall, *Amer. Journ. Med. Sci.*, cli., 1916.

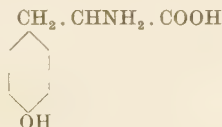
⁷ *Journ. Pharm. and Exper. Therap.*, vii., 1915; viii., 1916. Marine gives the maximum storage capacity of the normal gland as not more than 30 mgm. iodine (*Physiol. Abstracts*, June 1923). The thyroid of the goat is very rich in iodine (Arnold and Gley, *Journ. de Physiol.*, xxi., 1923).

organ. It is not retained by other organs, such as the liver and spleen. Administration of iodine increases the activity of the thyroid hormone, as shown by its effect in hastening metamorphosis in the tadpole. The iodine content is said to be increased markedly by administration of suprarenal substance deprived of adrenaline.¹ The activity of thyroid preparations is usually assumed to be parallel with their iodine content.² This varies greatly in different individuals, the variations being probably associated with the character of the food and the amount of iodine in it. But Pellegrini states that there is no definite relation between the amount of colloid and that of iodine in the thyroid. Preparations for medicinal purposes are usually standardised to a certain percentage of iodine (0.2 per cent.).

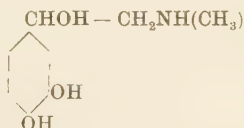
THYROXIN

Baumann's iodo-thyrin showed considerable variability in its iodine content and was evidently not a pure chemical substance. But in 1914 Kendall³ succeeded in isolating from the thyroid a substance in crystalline form, which contains 65.1 per cent. of iodine and has most of the active properties of thyroid juice. To this substance he has given the name *thyroxin*,⁴ having succeeded in identifying it chemically.⁵ Thyroxin has the formula $C_{11}H_{10}O_3NI_3$ = trihydro-tri-iodo oxyindol propionic acid. It occurs in various forms. In the keto form it crystallises in needles from acid solutions. In the enol form it is found in alkaline solutions, and from this an open-ring form (which is believed by Kendall to be that which occurs in the secretion) and an amino-hydrate form can be obtained. Its relations to tyrosine, adrenaline, and tryptophane are shown in the annexed diagrams:—

Tyrosine.



Adrenaline.



¹ Black, Hupper, and Rogers, *Amer. Journ. Physiol.*, lix., 1922.

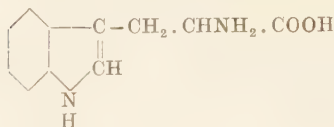
² Hunt and Seidell, *Journ. Amer. Med. Assoc.*, Oct. 1908; *Hygienic Lab. Bull.* 47, Washington, 1908; Aldrich, *Amer. Journ. Physiol.*, xxxi., 1912; Marine and Lenhart, *Arch. intern. Med.*, iii., iv., 1909; E. Roos, *Zeitschr. f. physiol. Chem.*, xxviii., 1899; A. Oswald, *Beitr. z. chem. Physiol.*, 1902; Cameron and Carmichael, *Journ. Biol. Chem.*, xlv., 1920, and xlvi., 1921.

³ *Journ. Biol. Chem.*, xx., 1914; *Collected Papers of Mayo Clinic*, viii., 1916; *Proc. Amer. Physiol. Soc.*, in *Amer. Journ. Physiol.*, xlv., 1918, and xlix., 1919; *Endocrinology*, i., 1917, and iii., 1919; *Harvey Lectures*, 1919-20.

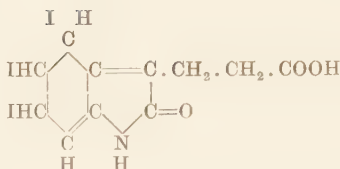
⁴ Abbreviated from thyro-oxy-indol.

⁵ *Journ. Biol. Chem.*, xxxix. and xl., 1919; the last paper in conjunction with Osterberg.

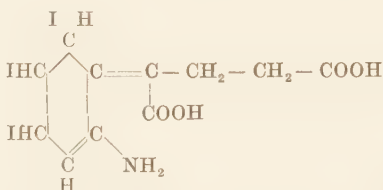
Tryptophane.



Thyroxin: keto form.



Thyroxin: open-ring form.



Kendall believes that thyroxin is responsible for all the characteristic physiological and therapeutic effects produced by thyroid juice or extract. But it does not cause increased contraction of the suspended intestinal muscular slip, which is actively excited by thyroid extract. The effect it produces on metamorphosis of tadpoles (p. 47) is, according to Kendall, due to the iodine in the molecule, not to the organic nucleus.¹

INFLUENCE OF THE NERVOUS SYSTEM ON THYROID SECRETION

It was thought by Cyon that vasodilator nerve-fibres pass from the recurrent laryngeal nerves to the thyroid gland. Ossokin and Asher² showed the gland to be supplied by both superior and inferior laryngeal, and also by pharyngeal, branches of the vagus. Vasoconstrictors and probably also secretory fibres pass to it from the sympathetic. The vasomotors at any rate are stimulated by adrenaline.³ H. Wiener⁴ found extirpation of the inferior cervical ganglion to be followed by atrophy of the gland and diminution of thyroglobulin in the thyroid of the same side. It is probable that the laryngeal nerves convey the sympathetic fibres to the gland. Asher and Flack⁵ thought the secretion to be directly influenced by nerve-fibres passing to the gland by the superior and inferior laryngeal nerves. They used as a test of the outpouring of secretion the increase of excitability of certain nerves (depressor and cardiac vagus), which, they state, is also produced by injection of thyroid extract into the blood. This, however, is certainly not a sure test of thyroid (see pp. 43, 44), and therefore, although it is not improbable that the secretion

¹ This appears to be related to the metabolic changes seen in mammals.

² *Zeitschr. f. Biol.*, lxiii., 1914.

³ Lee Gunning, *Amer. Journ. Physiol.*, xlv., 1917.

⁴ *Arch. f. exper. Path. u. Pharm.*, lxi., 1909.

⁵ *Zeitschr. f. Biol.*, lv., 1910. See also Levy, *Amer. Journ. Physiol.*, xli., 1916.

is under the influence of either the vagus or sympathetic, or both, further evidence is necessary before we can regard this as a proven fact. It has also been stated that the iodine content of a thyroid lobe is diminished as the result of excitation of the vagus of the same side; but this also needs confirmation. The fact that the thyroid will continue to function after transplantation even into a distant region, although necessarily deprived of its nerve-supply, shows that nervous influences are not essential to promote its secretion.¹

The view which was at one time held that the function of the thyroid is merely that of a destroyer of toxic substances circulating in the blood is no longer tenable. The same may be said for an old idea—resuscitated by Cyon—that the organ serves as a kind of shunt to regulate the flow of blood in the cranial cavity. This indeed has nothing to support it beyond the extreme vascularity of the gland and its position in close connexion with the carotids.

A current of action is obtainable from the thyroid when the cervical sympathetic is stimulated; and also by stimulating the splanchnics (but not if the suprarenal capsules had previously been removed), as well as from the action of an intravenous injection of adrenaline. No effect is got on stimulating the vagus.² In animals in which a phrenic nerve had been cut and joined up with the peripheral end of the cervical sympathetic, symptoms of hyperthyroidism were eventually produced which disappeared on removal of the thyroid of the same side.³ Other evidence in favour of the nervous control of the thyroid secretion is furnished by Cannon and Smith.⁴

The activity of the thyroid appears to be increased by external cold and by morphine, quinine, and strychnine:⁵ the action is in all probability produced through the sympathetic nervous system.⁶

¹ Manley and Marine, *Proc. Soc. Exper. Biol.*, xii., 1915; L. Loeb, *Journ. Med. Res.*, xxxix., 1918; E. Kummer, *Endocrinology*, i., 1917. Kummer found that such grafts would prevent *cachexia thyreopriva*.

² Cannon and Cattell, *Proc. Nat. Acad. Sci.*, Washington, 1916; *Amer. Journ. Physiol.*, xli., 1916.

³ Cannon and Fitz, *Amer. Journ. Physiol.*, xl., 1916. This result has not been obtained by others who have attempted the experiment (Langley, *Journ. Physiol.*, xxxi., 1904; Troell, *Allm. Svenska läkaret*, 1916—quoted from *Physiol. Abstracts*; Burget, *Amer. Journ. Physiol.*, xlv., 1917; Marine, Rogoff, and Stewart, *Amer. Journ. Physiol.*, xlv., 1918). Nevertheless a single positive result of this kind outweighs many negative findings.

⁴ *Amer. Journ. Physiol.*, lx., 1922.

⁵ C. A. Mills, *Amer. Journ. Physiol.*, xlv., 1918 (histological changes); C. Hart, *Arch. f. d. ges. Physiol.*, exci., 1922.

⁶ B. Romeis finds (tadpole test) that the activity of thyroxin is diminished considerably if it is allowed to stand with blood *in vitro*, and is rapidly abolished if introduced into the circulating blood (*Biochem. Zeitschr.*, cxl., 1923).

CHAPTER IV

THE THYROID (*continued*)

THE EFFECTS OF SURGICAL REMOVAL AND OF ATROPHY OR DEGENERATION OF THE THYROID: HYPOTHYROIDISM

Thyroidectomy. Schiff, who had previously (1856) performed the operation in various animals with incomplete results, was led in 1884 again to investigate the effect of thyroidectomy in animals:¹ he was also the first to attempt to combat the resulting symptoms by implantation of thyroid from an animal of the same species, and to suggest the parenteral or enteral administration of the gland, but made no experiments to test the suggestion. Schiff's extirpations probably in most instances, as the symptoms he records show, included the parathyroids. Gley drew attention to the importance of leaving at least two of these in order to study the effects of thyroidectomy alone. Subsequent observations on the subject are numerous, although some are contradictory. This is due mainly to the fact that differences are found with animals of different species, and that age introduces a material factor into the result; young animals being much more susceptible to thyroidectomy than adults, as they are also to parathyroidectomy.

Technique of Thyroidectomy.—N. M. Dott has given an account of the technique of the operation in the dog and cat, which should be perused in the original.² The most important precaution is to avoid removal of the parathyroids along with the thyroid lobes. This is best effected, in young animals, by slitting the fibrous sheath of the lobe along the ventral aspect and dissecting out the thyroid: the parathyroids are left in contact with the dorsal part of the sheath. Care must be taken to avoid the larger branches of the arteries, and especially the considerable anastomotic vessel which unites the superior and inferior thyroids: the parathyroid arterioles come off either from this or in close relation with it (see fig. 4). The steps of the operation are illustrated in fig. 10. All arterial branches passing into the thyroid proper are, of course, tied before removal of the gland.

Results of the Operation.—In young animals the most striking effect is marked retardation of growth.³ Ossification is delayed; the growth of the

¹ *Rev. méd. de la Suisse rom.*, 1884.

² *Quart. Journ. Exper. Physiol.*, xiii., 1923.

³ Hofmeister, *Fortschr. d. Med.*, x., 1892 (rabbits); A. Eiselsberg, *Arch. f. klin. Chir.*, xlix., 1895 (sheep, pigs, goats); Sutherland Simpson, *Quart. Journ. Exper. Physiol.*, vi., 1913 (sheep). H. R. Basinger, *Arch. intern. Med.*, xvii., 1916 (rabbits); Biedl, *Innere Sekretion*, iii. Aufl., Teil i., p. 185, 1916 (dogs). Sutherland Simpson finds that the effects on the growth of lambs, especially if the operation is delayed, are not always well marked as determined by size and weight, but the defects in development (*e.g.* growth of horns) are always manifest.

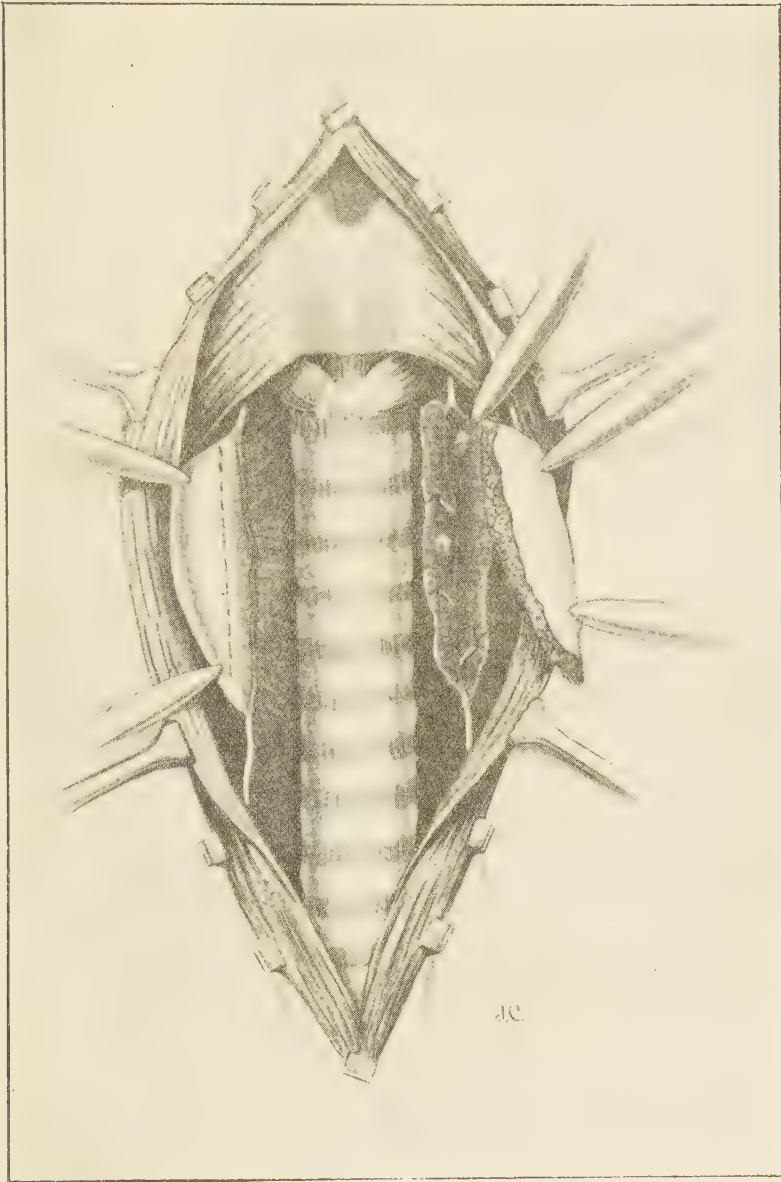


FIG. 10.—Thyroidectomy on the puppy (or kitten). About three times life size.
(N. M. Dott.)

The median incision is of ample length. The skin edges are excluded by a sterile towel folded round them and fixed with clips. The sterno-hyoid muscles have been separated and retracted, and the sterno-thyroids displaced with them. On one side the thyroid lobe is drawn to the surface; its stretched fascia capsule and the anastomotic vessel are seen. The dotted line indicates the line of incision of the capsule. On the opposite side the dissection is almost complete. The strip of posterior capsule left intact is represented. The thyroid arteries are seen entering it at either end, and the anastomotic vessel between them running in the fascia. The twigs from this vessel have been secured and tied close to the thyroid substance. The last remaining vessel is secured with the hæmostat at the upper pole, and the lobe is about to be removed. The two parathyroid glandules are seen lying intact in the fascial strip; it will be readily appreciated that their vascular supply has not been interfered with.

Neither the carotid sheath nor the recurrent laryngeal nerve has been exposed.



FIG. 11.—X-ray photographs of femur from three eight-week kittens of the same litter, of which A (male) was used as a control, B (female) was thyroidectomised, and C (female) was thyroid fed (6 cg. per kilo. per diem). The thyroid removal was effected and the thyroid feeding begun on the date these photographs were taken. The respective lengths of the femur are—A, 54 mm.; B, 51.5 mm.; C, 54 mm. A', B', and C' are from the same animals 51 days later. The respective lengths are now 71 mm., 56 mm., and 74 mm. In the control there is an increase in length of 17 mm.; this is taken as the standard increment; in the thyroidectomised animal the increase is only 4.5 mm. (= 73 per cent. deficiency); in the thyroid-fed animal the increase is 20 mm. (= 17 per cent. increment or acceleration). (N. M. Dott.)

intermediate cartilage being seriously interfered with, so that the long bones not only grow more slowly, but eventually attain much less than their normal adult length (fig. 11). The whole skeleton is, however, more or less involved, and the animals remain far smaller than controls from the same litter (figs. 12, 13, 14). The teeth are ill developed. The generative organs remain relatively small, and the ova and spermatozoa may not come to maturity. The pituitary becomes enlarged: its anterior lobe contains many colloid-filled vesicles. The aorta is often found to be atheromatous. The temperature of the body is lower than normal. The abdomen is generally swollen. The skin is thickened: the hairy covering is usually imperfectly developed, but in some animals (goats) they may be longer than in the normal animal. The



FIG. 12.—Normal control and two thyroidectomised rabbits from the same litter. Age 12 weeks. (H. R. Basinger.)

involution of the thymus is delayed or may not occur: the cortex of the suprarenals is somewhat enlarged. The central nervous system—especially the brain—is involved in the general arrest of development. In most young animals deprived of their thyroids there is a marked lack of intelligence:¹ this is manifested in the facial appearance, which is generally apathetic, so that the thyroidectomised animals have been described as “cretins.” Nevertheless Biedl found that in the young dogs operated upon by him no diminution of intelligence was manifest, although the head and face had an infantile character as compared with the controls. The same fact is noted for the pig by Eiselsberg.

¹ Sutherland Simpson found that thyroidectomised sheep took far longer to learn to find their way to food through a maze than controls (*Quart. Journ. Exper. Physiol.*, xiii., 1923).

At all ages there is marked diminution in basal and in general metabolism.¹



FIG. 13.—Three kids (triplets) of a horned nanny-goat: all three females. The middle one, which was originally smaller than the one on the right and about the same size as that on the left, was kept as a control, the other two being thyroidectomised on March 19, 1923, when 20 days old. The relative weights remained about the same until April 10, when the first photograph was taken, 22 days after the operation (A): at this date the weight of the control was found for the first time to exceed that of both the others. The second photograph (B) shows the same animals on June 20, 3 months after the operation. The larger size of the control animal and the greater development of the horns are striking features. (Sutherland Simpson.)

After complete thyroidectomy in adults creatin appears in the urine in considerable amount during fasting and in correspondingly diminished amount in

¹ Magnus-Levy, *Berlin. klin. Wochenschr.*, xxxi., 1895; *Zeitschr. f. klin. Med.*, xxxiii., 1897.

the muscles.¹ The limit of assimilation of carbohydrates is raised, but there is no glycaemia or glycosuria : indeed there may be less sugar than normal in the blood.² Adiposity may supervene, but there is at first usually wasting. The muscles lose tone and are weaker than in the normal animal. Muscular activity, as measured by a pedometer, is considerably diminished (Simpson). Regeneration of tissues is retarded. Anæmia is generally present, with lymphocytosis. Heat production is diminished. The body temperature is low : the power of heat regulation lessened.³ There is diminished excretion of CO_2 , especially when the external temperature is raised,⁴ and also a diminished consumption of oxygen, but the diminution of O_2 is less than that of CO_2 (Schenck). The



FIG. 14.—Twin lambs, female. The one on the right thyroidectomised at the age of 1 month, the other kept as control. The photograph was taken at the age of 1 year 4 months. (Sutherland Simpson.)

sexual functions are depressed. The nervous system is markedly affected, dullness and apathy being prominent symptoms. Many nerve-cells, especially those of the cerebral cortex, exhibit a shrunken appearance and present a strong contrast with those of the normal animal. There is a decrease in the Nissl granules in the cells of the cortex cerebri, of the cerebellum, of the medulla oblongata, and of the ventral horn of the cord.⁵ The skin is dry and often exhibits *cutis anserina* : the hair often tends to fall out, and the wool

¹ Frontali, *Arch. intern. de physiol.*, xiii., 1913 (dogs) ; A. Hunter, *Quart. Journ. Exper. Physiol.*, viii., 1915 (sheep).

² Bodansky, Sutherland Simpson, and Goldberg, *Proc. Soc. Exper. Biol.*, xx., 1922 (sheep).

³ Lorrain Smith, *Journ. Physiol.*, xvi., 1894 ; Schenck, *Arch. f. exper. Path. u. Pharm.*, xcii., 1922.

⁴ O. Hauri, *Biochem. Zeitschr.*, xcvi., 1919.

⁵ W. Edmunds, *Proc. Roy. Soc. Med.*, v., 1912 ; Isenschmidt, *Zeitschr. f. Path.*, xxi., 1918.

in sheep to be shed (Simpson). A myxœdematous condition of the integument was described in monkeys by Horsley,¹ Murray,² and Edmunds,³ and has also been affirmed both for herbivora⁴ and carnivora;⁵ but other experimenters, *e.g.* Munk,⁶ Biedl,⁷ Vincent and Jolly,⁸ Kishi,⁹ and Halpenny and Gunn,¹⁰ failed to observe this, and it seems doubtful if the puffiness which has been described as occurring in monkeys is of the same nature as the thickening of the integument seen in myxœdema of man.¹¹

Halpenny and Gunn removed the parathyroids along with the thyroid, and most of the authors quoted must have done the same, although they do not always specify if this was so or not. Several of Halpenny and Gunn's monkeys developed tetany, which was not diminished by administration of thyroid.

There is delay in the healing of fractures, and in degeneration and regeneration changes of cut nerve.¹² The red corpuscles of the blood are diminished in number and in amount of hæmoglobin, but the thrombocytes and leucocytes are increased, and with them the amount of fibrin.¹³ The iodine content of the blood rises after thyroidectomy, the rise being abolished by thyroid feeding.¹⁴ When the thyroid is removed from the amphibian larva, metamorphosis (of the tadpole into the frog) fails to occur. This will be referred to further when the effects of thyroid feeding on metamorphosis are considered.

After partial removal in mammals the thyroid readily regenerates; during regeneration there are signs of hyperactivity (see p. 19).

Hypothyroidism in Man.—Similar symptoms are observed in cases of spontaneous atrophy or fibrous degeneration of the glands in children (fig. 15), or after operative removal of the gland in growing individuals. There is defective growth, especially of the skeleton, the epiphyses being very late in appearing and the cartilage bones long remaining incompletely ossified and being short and thick: the tibiæ are curved: development of the generative organs is much delayed: the integument is swollen: the surface of the skin is dry and feels cold: the hair tends to fall out and become thin: the hairs are often lost from the outer third of the eyebrows (Hertoghe¹⁵): the eyelashes drop out: the nails become thin and brittle: the teeth tend to become loose and affected with caries: the face is pale and puffy: the abdomen is distended (pot-belly): the root of the nose depressed: the hands and feet broad, spade-like, and podgy. The mucous membranes of the mouth, nose, bladder, and urethra have an œdematous

¹ *Proc. Roy. Soc.*, xxxviii., 1884, and xl., 1886; *Brit. Med. Journ.*, 1885; *ibid.*, 1892; *ibid.*, 1896.

² *Diseases of the Thyroid Gland*, 1900.

³ *Journ. Path.*, various papers, 1886–1900.

⁴ G. Moussu, *C. r. soc. biol.*, iv., 1892.

⁵ J. J. Wagner, *Wien. med. Bl.*, 1884.

⁶ *Virch. Arch.*, cl., 1897.

⁷ *Innere Sekretion*, 1916.

⁸ *Journ. Physiol.*, xxxii., 1904, and xxxiv., 1906.

⁹ *Virch. Arch.*, clxxvi., 1904.

¹⁰ *Quart. Journ. Exper. Physiol.*, iv., 1911.

¹¹ Gley found in the rabbit that a myxœdematous condition took some months to develop (*C. r. soc. biol.*, lxxviii., 1910).

¹² Marinesco and Miura, *C. r. soc. biol.*, 1908 and 1910.

¹³ Albertoni, *Arch. intern. de physiol.*, xi., 1911.

¹⁴ W. A. Hudson, *Journ. Exper. Med.*, xxxvi., 1922.

¹⁵ A series of communications to the *Acad. roy. méd. Belg.*, 1895 to 1912.

appearance; the lips are thick and prominent; the tongue large and protruding. The mouth is generally open, and saliva dribbles from it. The fontanelles remain open. Dentition is generally abnormal, the teeth appearing late and being imperfectly calcified. The muscles are limp and weak. Both red and white blood corpuscles are diminished in number; the coagulability of the blood is decreased. Constipation frequently occurs. The complexion is sallow; the eyes dull and expressionless. There is always a marked diminution in general and basal metabolism; the gaseous exchanges being greatly reduced in all forms of hypothyroidism. Deaf-mutism is common. The highest functions of the nervous system remain undeveloped, the child becoming idiotic: this seems to be due to an arrested development of the cells of the cortex cerebri. In lesser degrees of the affection the subject is feeble-minded. There is said to be an unusual susceptibility to infectious diseases, to which the majority of cretins succumb in early life (M'Carrison).

The above combination of symptoms forms the condition known as *cretinism*.¹ This may be either sporadic or endemic. The former is generally associated with absence or early atrophy of the thyroid, and is usually more amenable to thyroid treatment; the latter with goitrous degeneration. Of endemic cretinism, according to M'Carrison,² there are in the Himalayan valleys two types, the myxœdematous and the nervous; the latter is presumably associated with changes in the parathyroids, being accompanied by many of the symptoms of tetany. In the former the parathyroids are unaltered. This is the type chiefly met with in Europe.

The symptoms do not show themselves until some little while after birth, in spite of the absence or atrophic condition of the thyroid. The absence appears to be compensated, for a time at any rate, by autacoids conveyed from the mother's thyroid to the child; perhaps before birth through the placenta and after birth through the milk: but Sutherland Simpson found



FIG. 15.—Typical cretin. (Victor Horsley.)

¹ For accounts of cretinism (with literature), see W. Scholtz, in *Ergebn. d. inn. Med.*, 1906 and 1909; R. M'Carrison, *The Thyroid Gland*, 1917; N. W. Janney, in *Endocrinology and Metabolism*, edited by L. F. Barker, 1922; and M. B. Gordon, *Endocrinology*, vi., 1922. According to Gordon, only the sporadic type occurs in America, although goitre, which is often, in Europe, associated with cretinism, is fairly common.

² *Lancet*, ii., 1908.

that even in suckling lambs the effects of thyroidectomy were seen; and Tauberg denies the passage through the placenta.¹

Congenital myxœdema is almost always associated with entire absence of the thyroid (athyrosis), although the parathyroids are usually normal.²

If in the adult subject either thyroid atrophy occurs or such degenerative changes take place in the gland as materially affect its functions, the condition known as *myxœdema* (or *myxœdema adultorum* to distinguish it from the corresponding affection of the child) becomes manifested (fig. 16). This condition was first described by Gull,³ and recognised by him



FIG. 16.—Myxœdema adultorum. Two photographs of the same individual, A taken before and B subsequent to the development of myxœdema. (Victor Horsley.)

to be a cretinoid condition of adult life; and subsequently by Ord,⁴ who gave the name to the disease on the supposition that the œdematous condition of the integument is of a mucinous nature; this, however, seems doubtful. Ord showed that it is associated with changes in the thyroid, which is greatly diminished in size if not altogether atrophic. Myxœdema is much more common in women than in men, and commonest in women from 30 to 40 years of age.⁵ The symptoms are similar to those described under hypothyroidism (p. 32). The affection is characterised by thickening and swelling of the integument, which pits on pressure, the pitting disappearing on relaxing the pressure; by the skin becoming dry and exhibiting cutis anserina, especially in certain parts; by the hairs falling out; by a low body temperature; and by mental dullness and general impairment of

¹ *Acta med. scand.*, lvi., 1922.

² F. Pineles, *Wien. klin. Wochenschr.*, 1902 and 1904. See, on myxœdema in children and adolescents, Hutchison, *Brit. Journ. of Children's Dis.*, vi., 1909.

³ *Trans. Clin. Soc.*, vii., 1874.

⁴ *Med. Chir. Trans.*, lxi., 1878. See also "Report on Myxœdema" by a Committee of the Clinical Society, 1888.

⁵ W. Hale-White, *Lancet*, i., 1913.

sensibility. The muscles are also affected by the œdematous change: muscular weakness is an early sign.

A similar condition is not uncommon in "goitre" districts, and is then usually associated with degenerative changes of the thyroid. Such cases are usually known as endemic cretinism (fig. 17). They are often characterised by a depression of the root of the nose. In cases of myxœdema in the human subject Mott has described general chromatolysis of nerve-cells of subacute character.¹ Both in spontaneous and in operative myxœdema the metabolic processes are diminished in activity, so that although less food is taken the body-weight may increase. Regenerative changes in the tissues also occur more slowly. There is usually a considerable deposition of fat, especially under the skin: the obesity, which may be extreme, is

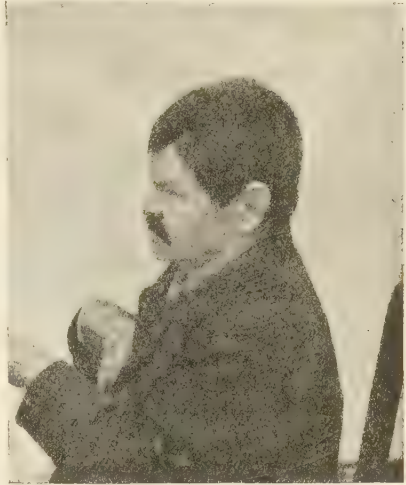


FIG. 17.—A case of endemic cretinism. (E. Bircher.) The characteristic depression of the root of the nose is seen.



FIG. 18.—A case of post-operative myxœdema (cachexia strumipriva) in a 26-year-old woman. (Bruns.)

as the result of surgical removal of the thyroid in man (fig. 18). This was first apparent as the result of the effects of operation for goitrous

not confined to any particular region.² The activity of the sexual functions is diminished (in both sexes). There is a diminution in the amount of oxygen consumed and in the amount of nitrogen excreted. There is increased tolerance for sugar, so that a considerably larger amount than usual (as much as 300 grams) may be taken without producing glycosuria. When glycosuria occurs it is not excessive. Janney and Isaacson³ found a 25 per cent. diminution of blood sugar to follow thyroidectomy.

Symptoms similar to those of myxœdema are produced

¹ F. W. Mott, *Proc. Roy. Soc. Med.*, vi., 1913, and x., 1917.

² Pituitary obesity chiefly affects the lower part of the body.

³ *Proc. Soc. Exper. Biol. and Med.*, xiv., 1917.

tumours.¹ The Reverdins spoke of the condition as *operative myxædema*; Kocher termed it *cachexia strumipriva* (*thyreopriva*). It began to show itself at a variable period after operation—from a few days to months or even years—and was more readily produced in young than in older subjects. It was sometimes accompanied by symptoms of tetany: when present these symptoms are presumably referable to involvement of parathyroids. The patients rarely survived the complete loss of the thyroid for more than seven years. To prevent ultimate ill-effects at least one-fourth of the organ must be left.²

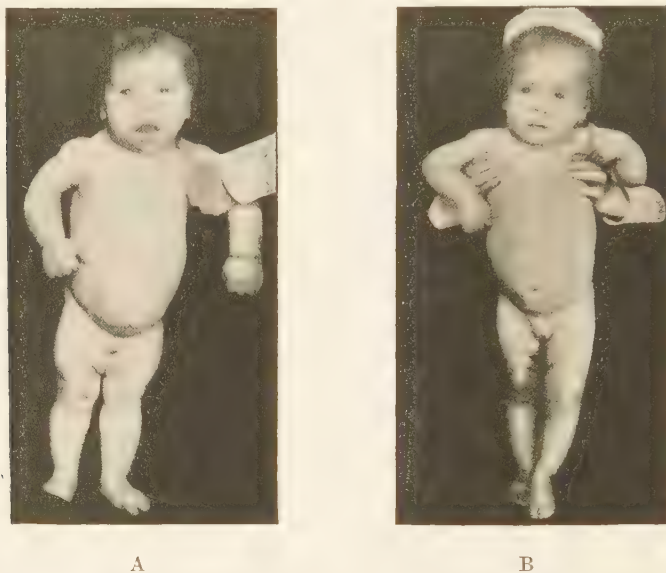


FIG. 19.—Cretinous child (A) before and (B) after treatment with thyroid.
(Byrom Bramwell.)

The above symptoms, whether due to congenital atrophy or to operative removal, can be allayed or entirely removed by successful implantation of pieces of thyroid (Schiff)³—an operation which has, however, rarely succeeded in man—or by administration of thyroid substance or extract either hypodermically⁴ or by the mouth.⁵ Patients suffering from the effects of loss of thyroid secretion, whether this takes the form of cretinism, myxædema, cachexia strumipriva, or endemic goitre, can be completely restored to health and kept normal for apparently any length of time by buccal administration of the gland or its

¹ J. L. and A. Reverdin, *Rev. méd. d. l. Suisse rom.*, 1883; Th. Kocher, *Arch. f. klin. Chir.*, xxix., 1883.

² Th. Kocher, *Arch. f. klin. Chir.*, lxiv., 1901; *Centr. f. inn. Med.*, 1906.

³ *Arch. f. exper. Path. u. Pharm.*, xviii., 1884. See also V. Horsley, *Brit. Med. Journ.*, i., 1885, and a series of communications by Cristiani in *C. r. soc. biol.*, 1894 to 1905.

⁴ G. R. Murray, *Brit. Med. Journ.*, 1891, 1892.

⁵ E. L. Fox, *Brit. Med. Journ.*, 1892; H. Mackenzie, *Lancet*, 1892; Howitz, *Ugeskr. f. Laeger*, 1892.

extracts (see figs. 19, 20, 21). The physical defects are remedied more readily than the mental defects, but these also respond to treatment. The body temperature rises, the patient becomes brighter in appearance; the skin softer and less puffy; the abdomen less distended. The earlier treatment is commenced, the better are the results. The sporadic type is more amenable than the endemic. If the treatment is intermitted the symptoms almost at once begin to reappear. The effects are therefore obviously due to the loss of an autacoid contained in the internal secretion. This autacoid in some way affects the metabolic processes of the body, either directly or indirectly promoting the



FIG. 20.—Myxœdema of adult (A) before and (B) after treatment with thyroid. (Andersson.)

nutrition of the tissues, and especially facilitating the functions of the cells of the nervous system, particularly those of the cerebral cortex.

G. R. Murray¹ gives the history of the first case of myxœdema treated with thyroid. The patient, a woman aged forty-six, was treated continuously and successfully with thyroid until her death, aged seventy-four. Th. Kocher² tried thyroid implantation or grafting in numerous cases of cretins, cachexia strumipriva, and myxœdema. Out of 93 such cases, 23 were entirely cured and 18

¹ *Brit. Med. Journ.*, i., 1920.

² *Arch. f. klin. Chir.*, cv., 1914. See further, on the transplantation of thyroid in man, H. Cristiani in *C. r. soc. biol. and Journ. de Physiol.* (1894 to 1906); E. Payr, *Arch. f. klin. Chir.*, lxxx., 1906; C. Goodman, *Amer. Journ. Med. Sci.*, clii., 1916; and A. Kocher, *Brit. Med. Journ.*, ii., 1923. Kocher states that the best preparation for grafting is a piece of an exophthalmic goitre. Thyroid must be administered both before and for some time after the graft has been planted: otherwise the organism absorbs the graft before it has had time to "take." In animals, L. Loeb, *Journ. Med. Res.*, xxxix., 1918, and *Journ. Exper. Med.*, xxxi., 1920. J. Lockhart Gibson (*Brit. Med. Journ.*, i., 1893) tried grafting a lamb's thyroid in a case of endemic cretinism in a child—apparently with some success—although it is not possible that such a graft would be permanent. Kocher also got apparently successful results from sheep and goat thyroid implanted in man. See also Bettencourt and Serrano, *Progrès méd.*, xviii., 1890 (graft of sheep thyroid).

showed improvement, but needed buccal administration of thyroid. Kocher obtained most success from implanting pieces of thyroid into the spleen and bone-marrow (upper end of tibia). The basal metabolism which is lowered in myxoedema can be brought up to normal by thyroid administration.¹

Endemic Goitre.—This usually takes the form of a large, firm, non-pulsating tumour in front of the neck (fig. 21), extending frequently to the sides, due to an enlargement of the thyroid gland, the vesicles of which are greatly hypertrophied and distended with colloid. It is common in certain districts, in England in Derbyshire ("Derbyshire neck") and in Norfolk: in certain villages of Switzerland and of the Himalayas and in the region of the Great Lakes of North America. Although there taking as a rule a less pronounced



FIG. 21.—A case of endemic goitre (A) before and (B) after treatment with thyroid. (Bruns.)

form, it is found not only in man but in domestic animals and even in fish.² The cause has been usually ascribed to a peculiarity in the drinking water, and it must be set down probably to a water-borne germ.³ Although such a germ has not yet been successfully isolated, M'Carrison found that cases of endemic goitre improved when treated with a vaccine from organisms isolated from the bowel, as well as with pure cultures of bacillus coli and of streptococcus. Administration of small doses of iodide is said to prevent its occurrence in places where goitre is endemic.⁴ Endemic goitre occurs six times as often in females as in males. It shows a strong congenital tendency, the children of goitrous parents being frequently goitrous; but this may only mean that they have been subject to similar conditions.

¹ Means and Aub, *Arch. intern. Med.*, xxiv., 1919.

² Marine and Lenhart, *Journ. Exper. Med.*, xii., xiii., and xix., 1910–1914.

³ R. M'Carrison, *Proc. Roy. Soc.*, B, 1909, 1911, 1915. See also *The Etiology of Endemic Goitre*, 1913; *Lancet*, 1913 and 1914; *The Thyroid Gland*, 1917.

⁴ Kimball, Rogoff, and Marine, *Coll. Pap. H. K. Cushing Lab.*, Cleveland, vi., 1918–20. Also (with Stewart and Lenhart) in *West. Reserve Univ. Bull.*, xxvi., 1923.

It has been noted that in goitre districts certain sources of water are peculiarly liable to be associated with the occurrence of goitre, and that water from these sources will produce goitre in animals. The agent which causes this will pass through a Berkefeld filter, but not through a dialyser, and is destroyed by a temperature of 80° C.¹

Monge² states that a form of endemic goitre which prevails in parts of Brazil is carried by a trypanosome transmitted by an insect. But he was unable to find this organism in the blood of cases of a similar disease in the goitre belt of Peru.

Burget³ found in rats that excess of protein in the food causes enlargement of thyroid in adult animals but not in young ones. Although such enlargement is produced at all ages by keeping the animals under unhygienic conditions, the addition to the food of faeces of goitrous individuals gave in his hands a negative result. Nor was any change produced in the structure of the organ on cutting the cervical sympathetics, although there is evidence to show that secretory influences pass to the gland through these nerves.

An enlargement of the thyroid—not, however, of the same nature as endemic goitre—can be produced in puppies by excess of butter and other fats in the food, while cod liver oil affords protection against enlargement due to insanitary conditions.⁴ The thyroid is also enlarged in inanition, but may contain less colloid than normal.⁵

Enlargement of the thyroid such as occurs in endemic goitre (fig. 21) in spite of a great increase in volume of the gland, is commonly attended by symptoms of hypothyroidism; not, as might have been expected, by those of hyperthyroidism.⁶

The enlargement generally takes the form of a diffuse hypertrophy: the individual follicles increase in size: new follicles may also become formed. There is nearly always a tendency for colloid to accumulate. This ultimately causes enormous distention of the vesicles and flattening of their epithelium (fig. 22), which may eventually undergo almost complete degeneration. A characteristic degeneration of the arteries of the gland has been described.

Whilst the above are the usual changes found in endemic goitre, many exceptions are met with. One would expect the enlarged gland to yield an excessive amount of secretion to the blood, but this appears not to be the case, although endemic goitre is occasionally characterised in its early stages by symptoms suggestive of hypersecretion and resembling some of those seen in incipient exophthalmic goitre (p. 50). More often these symptoms

¹ M. Wilms, *Deutsch. med. Woch.*, 1910; E. Bircher, *Zeitschr. f. Chir.*, ciii., 1910, and *Ergeb. d. Chir. u. Orthopæd.*, 1913; B. Breitner, *Wien. klin. Wochenschr.*, 1912.

² *Cron. méd.*, Lima, 1920.

³ *Amer. Journ. Physiol.*, xlv., 1917.

⁴ Cf. R. M'Carrison, *Ind. Journ. Med. Res.*, vii., 1920, and xi., 1923; *Brit. Med. Journ.*, 1922. E. and M. Mellanby, *Journ. Physiol.*, lv., 1921, *Proc. Physiol. Soc.*

⁵ Vincent and Hollenberg, *Journ. Physiol.*, liv., 1921.

⁶ When the enlargement is the result of malignant cell-proliferation (carcinoma or sarcoma), the functions of the organ may still be carried on actively. It is indeed a significant fact in connexion with the genesis of malignant tumours, that when in such cases the whole of the thyroid is removed by the surgeon, should there be any metastatic growths elsewhere, e.g. in the liver, the usual symptoms of operative myxœdema do not show themselves.

of hyperthyroidism are absent from the first, and always eventually; the appearances which show themselves are unquestionably symptomatic of hypothyroidism. This must mean that even if the secretion is being produced in abundance it is not of a normal character, the normal autacoid being either absent or deficient in quality. Perhaps the enlargement of the gland represents an attempt by nature to compensate for such deficiency.¹

Mott and Kojima² have shown that thyroid deficiency is common in certain kinds of insanity, and that it is accompanied by atrophy and fibrous and lymphoid infiltration of the gland. It is associated with extensive chromatolysis throughout

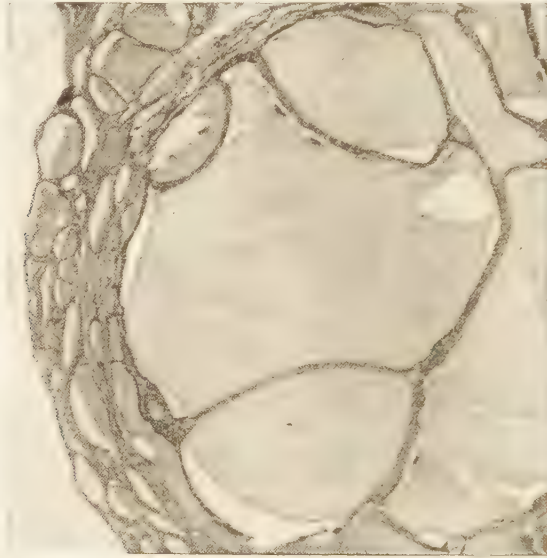


FIG. 22.—Section of thyroid from a case of endemic goitre. Magnified 50 diameters. Notice the enormous size of some of the colloid-filled vesicles.

the central nervous system and sometimes in the sympathetic ganglia.³ Other forms of insanity, especially in their earlier stages, suggest overactivity of the gland.⁴

The existence of large amounts of colloid in the tumours of endemic goitre, which are nevertheless accompanied by symptoms pointing to hypothyroidism, raises grave doubts as to whether the colloid met with in the vesicles is the true secretion—in the sense of being the physiologically active secretion—of the gland. These doubts are accentuated by the fact that in portions of thyroid that are unquestionably superactive—as occurs when a large part of the gland is removed

¹ D. Marine, *Cleveland Med. Journ.*, Feb. 1907, and *Johns Hopkins Hosp. Bull.*, xviii, 1907. On the relation of iodine to the structure of the goitrous thyroid, see Marine and Williams, *Arch. intern. Med.*, 1908.

² *Proc. Roy. Soc. Med.* (Section Psych.), viii, 1915.

³ F. W. Mott, *ibid.* (Section Path.), x., 1917; M. Kojima, *ibid.*

⁴ Dercum and Ellis, *Journ. Nerv. and Mental Dis.*, xl., 1913.

and a small portion only remains—no colloid collects in the vesicles, which tend to lose their closed character (fig. 7, p. 19) and are converted into open intercommunicating spaces, the fluid in which is not of the nature of the colloid of the normal gland. Nor apparently does it accumulate in the spaces, but seems to find a ready escape into the blood. Moreover, the amounts of colloid and iodine in the gland do not always run parallel.¹

The colloid which accumulates in the vesicles in endemic goitre—although in such cases there is evidence of depressed thyroid activity—nevertheless contains a considerable proportion of iodine, more sometimes than is the case with the normal gland. If, as some authorities hold, the activity of normal thyroid secretion is parallel with its iodine content, the inactivity of the colloid of endemic goitre is difficult of explanation, unless it be that its absorption into the blood is in some manner interfered with.

¹ Claude and Blanchetière, *Journ. de physiol.*, xii., 1910. See also p. 23.

CHAPTER V

THE THYROID (*continued*)

EFFECTS OF INCREASE OF THYROID SECRETION : HYPERTHYROIDISM

THE effects of a too great amount of the thyroid autacoids in the circulating blood can be investigated either by their introduction directly into the circulation or indirectly by other channels, such as the alimentary canal ; or by studying the symptoms of affections in which there is reason to believe that an excess of these autacoids is being secreted by the gland.

EFFECTS OF ADMINISTRATION OF THYROID EXTRACT OR JUICE

Effects of Intravascular Injection.—The immediate result of intravenous injection (fig. 23) is, in most animals, to produce a marked but evanescent fall

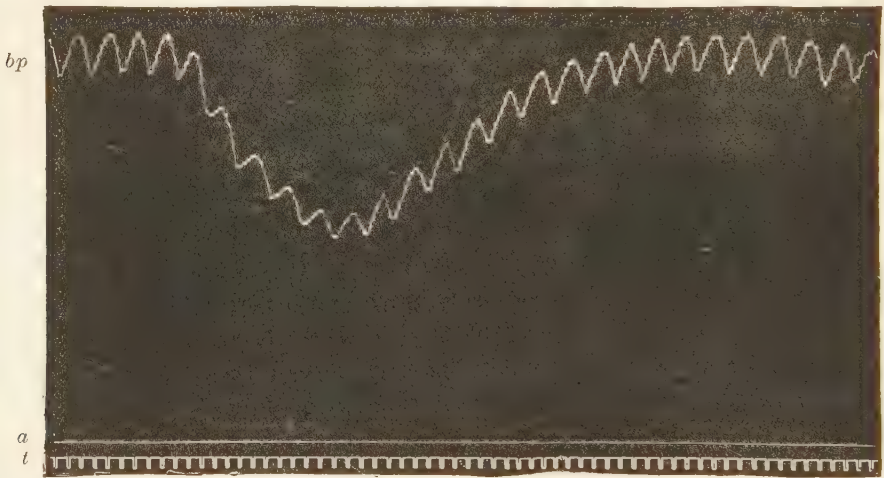


FIG. 23.—Effect upon the blood-pressure of injecting thyroid extract intravenously.
bp., arterial pressure ; *a.*, abscissa ; *t.*, time in one-second intervals. (From the *British Medical Journal*, Aug. 10, 1895.)

of blood-pressure, which is mainly due to dilatation of the peripheral vessels. This effect is probably due to a specific chalone, although somewhat similar results are obtained with extracts of many other organs.¹

The fall of blood-pressure caused by thyroid extract is often preceded by a slight rise. In rabbits, only this rise usually occurs. The fall is just as

¹ Vincent and Sheen, *Journ. Physiol.*, xxix., 1903. v. Fürth and Schwarz (*Arch. f. d. ges. Physiol.*, cxxiv., 1908) believe it to be choline.

well marked after administration of atropine as before : it is therefore not due to vagus action.

Extract of thyroid contains an excitant of intestinal muscle (fig. 24). This owes the effect not to thyroxin, the chief physiological principle of the secretion, but to some other unknown substance, which according to F. S. Hammet is increased in amount at certain periods of life (white rat), viz. at birth, weaning, puberty, and end of rapid growth.¹

Asher² found that the prior injection of thyroid extract in the rabbit increases the excitability of the splanchnics, of the cardiac vagus, and of the depressor.³ I was not myself able to confirm this result for the depressor either in the rabbit or in the cat or dog, although in the last two, if depressor fibres are stimulated

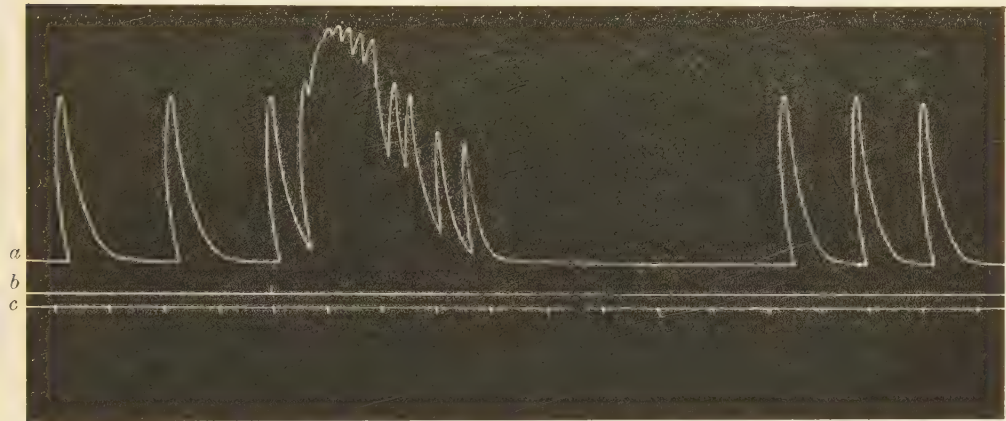


FIG. 24.—Effect of a small dose of thyroid extract upon the contractions of an isolated strip of intestinal muscle from cat's ileum.

at the same time that thyroid extract is injected into a vein, the fall of blood-pressure is greater than with either of these by itself. This is, however, an effect of summation, as is shown by the circumstance that in those cases in the rabbit in which a slight rise is produced by the thyroid extract instead of a fall, the combined effect of depressor and thyroid extract is less than that of the depressor alone.

Oswald⁴ found this effect (increased sensitivity of autonomic nerves) to be caused in the rabbit by iodothyrim and iodothyroglobulin. He states that it appears within one to two minutes and lasts forty minutes or more after the injection. He found the effect on the depressor nerve less marked than on the vagus, and states that these substances also accentuate the action of adrenaline. Albertoni⁵ got a similar effect with small doses of thyroid extract, but a diminution

¹ *Amer. Journ. Physiol.*, lx., 1921.

² Asher and Flack, *Zentralbl. f. Physiol.*, xxiv., 1910 ; Asher and v. Rodt, *ibid.*, xxvi., 1912.

³ v. Cyon and Oswald obtained a similar effect on the depressor (*Arch. f. d. ges. Physiol.*, lxiii., 1901).

⁴ IX. *Congrès intern. de physiol.*, in *Arch. intern. de physiol.*, xiv., 1913, p. 43.

⁵ *Arch. ital. de biol.*, lxv., 1916.

of excitability with large doses. Coronedi¹ found the excitability of the vagus diminished after thyro-parathyroidectomy and restored by thyroid feeding.

Considerable doubt is thrown on most of these results by the experiments of Lieb and Hyman,² who find a gradual increase of excitability of autonomic nerves to occur even without thyroid administration. They employed small and constant doses of adrenaline as tests of excitability of the sympathetic. Dryerre,³ who has pursued similar investigations in my laboratory, finds that if proper precautions are taken to ensure that the nerve which is being stimulated remains throughout under the same conditions, the results of injection of extracts are entirely negative.

Demoor⁴ found that thyroid extract from the dog perfused through the surviving heart (rabbit) produces at first an excitation followed by a depression and eventually stand-still. But if the rabbit had been previously immunised against dog's thyroid, there is only excitation, which is more pronounced.

Thyroid extract which, as already stated, itself stimulates intestinal muscle, does not, if applied immediately prior to the addition of adrenaline to the Ringer's fluid in which the muscle is suspended, increase the sensitiveness of that muscle to the (inhibitory) action of adrenaline.

*Effects of Thyroid Feeding: Hyperthyroidism.*⁵—Given by the mouth in the human subject, thyroid extract produces lowering of the blood-pressure.⁶ Large doses are followed by tachycardia (rapid pulse),⁷ often with some irregularity; nervous excitability; flushing of the skin, with feeling of heat and increase of perspiration; other secretions have also been found to be increased.⁸ In extreme cases there may be exophthalmos and other effects referable to cervical sympathetic excitation, such as dilatation of the pupil and (in animals) retraction of the third eyelid, psychical excitement, sleeplessness, tremors of the limbs—in short, many of the symptoms of exophthalmic goitre.

Effects on Growth and Metabolism.—The addition to the food of even a small amount of thyroid gland has the effect of increasing nitrogenous metabolism, as shown by the increase of nitrogen in the urine. This is accompanied by a corresponding increase in food consumption. Some of the additional nitrogen thus ingested is retained in the body, but this is compensated for by increased fat consumption, so that the difference in growth curve of the thyroid-fed animals and the controls is but slight. With larger doses of thyroid there

¹ *Arch. intern. pharm.*, xxiii., 1913.

² *Amer. Journ. Physiol.*, lxiii., 1922.

³ *Trans. XI. Physiol. Congress*, in *Quart. Journ. Exper. Physiol. Suppl.* Vol., 1923.

⁴ *C. r. soc. de biol.*, lxxxv., 1921.

⁵ On the production of hyperthyroidism in animals, see R. Farrant, *Brit. Med. Journ.*, 1913 and 1914.

⁶ In diabetic subjects it is stated that the opposite effect is obtained.

⁷ Carlson, Rooks, and M'Kie failed to get this in animals (*Amer. Journ. Physiol.*, xxx., 1912), and Kendall got no effect from thyroxin feeding, but when amino-acids were administered simultaneously he found the pulse-rate to be enormously increased (*Boston Med. and Surg. Journ.*, clxxv., 1916).

⁸ Marbé (intestinal), *C. r. soc. biol.*, 1912; Kojima (pancreatic), *Quart. Journ. Exper. Physiol.*, xii., 1920.

soon ensues loss of weight, due both to increased nitrogen elimination and loss of fat. There is also a greater respiratory exchange, and the basal metabolism is markedly increased whether the carbohydrate storage has been previously depleted or not.¹ After thyroid administration, both in man and animals, it has not been possible to determine the presence of active thyroid material in the blood.²

Although relatively large doses of thyroid increase metabolism and diminish the weight of thyroid-fed animals, small amounts cause an increase in weight, apparently by leading to consumption of a greater amount of food, which more than compensates for the slight increase of metabolism caused by the thyroid.³ Thyroid secretion is the most powerful stimulant of body metabolism known. The increase of basal metabolism which it produces is of interest clinically because such increase is characteristic of exophthalmic goitre, and this is believed to be accompanied by excessive thyroid secretion.⁴ An increase of basal metabolism also occurs when thyroxin is administered, and directly as the dose supplied: thus if 0.33 mg. thyroxin causes an increase of 2 per cent., 0.66 mg. will cause 4 per cent., and 3.3 mg. 20 per cent.⁵

Most of the effects both of thyroidectomy and of thyroid feeding are probably related to the effects on metabolism.⁶ According to Hewitt, both large and small doses cause an increase of NH_3 in the urine. Hirsch and Blumenfeld⁷ found thyroid feeding of growing animals to cause not an increase but a decrease in metabolism, but this statement is opposed to most other evidence on the subject.

Feeding with thyroid gland produces complete disappearance of glycogen from the liver even when the animals (rats and cats) are kept on a diet rich in carbohydrates. Nevertheless no sugar appears in the urine,⁸ but the carbohydrates which are poured into the blood become oxidised in the tissues. Removal of the thyroid and parathyroids in rats, which survive the complete operation longer than most animals, does not greatly affect metabolism, which is at first diminished and later again increased. The curves of the CO_2 output and of the O_2 intake do not essentially differ from those of a normal animal.⁹ Injection of thyroid extract into hibernating animals greatly increases their metabolism and often causes them to wake up.¹⁰

Both E. R. Hoskins¹¹ and P. T. Herring¹² noticed great enlargement of the heart, liver, kidneys, pancreas, ovaries, testes, and suprarenals in rats fed with

¹ Asher and Horrisberger, *Biochem. Zeitschr.*, cxxi., 1921.

² Reid Hunt, *Amer. Journ. Physiol.*, lxiii., 1923.

³ Schafer, *Quart. Journ. Exper. Physiol.*, v., 1912; Hewitt, *ibid.*, viii., 1914.

⁴ See on this subject Meakins and Davies, *Edin. Med. Journ.*, 1922; and C. M. and D. Wilson, *Lancet*, 1920.

⁵ E. C. Kendall, *Endocrinology*, iii., 1919; and *Harvey Lectures*, 1921. Plummer (quoted by Kendall) found that in a man weighing 150 lbs., 0.33 mg. thyroxin increased basal metabolism 2 per cent.

⁶ Jarisch, *Arch. f. d. ges. Physiol.*, clxxix., 1920.

⁷ *Zeitschr. f. exper. Path. u. Therap.*, xix., 1918.

⁸ Cramer and Krause, *Proc. Roy. Soc., B*, lxxxvi., 1913. M. Parhon (*Journ. de physiol.*, xv., 1914) obtained a diminution of liver-glycogen in thyroid-fed rabbits.

⁹ Cramer and McCall, *Quart. Journ. Exper. Physiol.*, xi., 1917. Their conclusions are confirmed by Herring, *ibid.*

¹⁰ P. Schenck, *Arch. f. d. ges. Physiol.*, cxcvii., 1922.

¹¹ *Journ. Exper. Zool.*, xxi., 1916.

¹² *Quart. Journ. Exper. Physiol.*, xi., 1917.

thyroid. Herring states that the heart and kidneys may be more than trebled in weight, and the suprarenals and pancreas more than doubled. The animals often died suddenly. Hewitt¹ confirmed these observations. He found that there was diminution in size of the thyroid itself. On stopping the administration of thyroid the organs gradually return to their normal size. The increase of basal metabolism in hyperthyroidism may be 100 per cent. or more. The blood-sugar content is also increased, whilst there is a diminished tolerance for carbohydrate food.² There is considerable disturbance of the digestive system and often severe diarrhoea. Most animals are less susceptible to the effects of thyroid feeding than man, and carnivora less than herbivora.³

The addition of fresh thyroid to a meat-free diet causes marked rise in N-excretion, accompanied by diuresis. The N is chiefly due to urea, but there is also an increase in NH_3 , and creatine appears in the urine.⁴

The changes observed by Hoskins and by Herring as the result of thyroid feeding are similar to those found by Hatai⁵ as the result of subjecting rats to frequent and severe exercise. Female rats appear more susceptible than males. In growing females the development of the uterus is checked by thyroid feeding. When thyroid is administered to rats along with a diet deficient in vitamins growth is markedly retarded; the combined effects usually prove fatal.⁶

The hypertrophy of the suprarenals chiefly affects the cortex, but there is evidence that the absolute amount of adrenaline is increased by thyroid feeding, whereas with thyroid deprivation (thyroidectomy) it is decreased (see fig. 34, p. 64, from Herring). But the increase of rate of the heart produced by thyroid administration is not wholly due to increase of adrenaline secretion, for it occurs even if the suprarenal capsules are removed: moreover, the direct effect comes on more slowly and lasts much longer than the adrenaline effect (Cannon and Smith).⁷

¹ *Quart. Journ. Exper. Physiol.*, xii., 1920. A. T. Cameron and J. Carmichael have obtained similar results in rats both with thyroid and with thyroxin feeding (*Amer. Journ. Physiol.*, lviii., 1921).

² M'Caskey, *Endocrinology*, iii., 1919. Marie Krogh (*ibid.*) found an increase of 80 per cent. basal metabolism in exophthalmic goitre, which is presumed to be associated with hyperthyroidism, and a decrease of 40 per cent. in myxoedema. See further on the subject of metabolism in hyperthyroidism, E. Mayerle, *Zeitschr. f. klin. Med.*, lxxi., 1910; Sandiford, *Endocrinology*, iv., 1920; and H. F. Stoll, *Boston Med. and Surg. Journ.*, clxxxvii., 1922.

³ Carlson, Rooks, and M'Kie, *Amer. Journ. Physiol.*, xxx., 1912; R. H. Cunningham, *Journ. Exper. Med.*, iii., 1898; W. Edmunds, *Journ. Path. and Bact.*, xxi., 1916; M. Kojima, *Quart. Journ. Exper. Physiol.*, xi., 1917 (rat).

⁴ Krause and Cramer, *Proc. Physiol. Soc.*, in *Journ. Physiol.*, xlv., 1912.

⁵ *Anat. Record*, ix., 1915.

⁶ Cameron and Moore, *Trans. Roy. Soc. Canada*, 1921. See further, on the influence of thyroid feeding on the growth of the body and on various organs of the white rat, Cameron, Carmichael, and Sedziak, in *Amer. Journ. Physiol.*, lviii., 1921; and Cameron and Carmichael, in *Journ. Biol. Chem.*, xlv., 1920, xlv., 1921, and in *Trans. Roy. Soc. Canada*, 1922. Cameron and Carmichael found a decrease in growth of rats and rabbits when fed with thyroid, which was more or less parallel with the iodine content of the preparations employed.

⁷ *Endocrinology*, iv., 1920; *Amer. Journ. Physiol.*, lx., 1922.

These observers used the denervated heart (cat) so as to eliminate any effect produced through the central nervous system. They obtained similar results from gentle massage of the thyroid and from stimulation low down of the cervical sympathetic; the latter being ineffective if the thyroid is removed—indicating that the result is due to increased secretion of thyroid juice.

Shumway¹ states that the addition of thyroid extract to hay infusion greatly increases the rate of multiplication of *Paramecium*. No other gland extract had a similar effect. G. T. Cori confirms this for thyroid extract, but found that thyroxin only produces a slight effect.²

It has been found that regeneration of tissues occurs more rapidly if thyroid extract is administered.³ This is also true of the union of fractured bone. Carrell noticed that the growth of surviving tissues in culture media was expedited if a small amount of thyroid extract was added.⁴ Walter states that nerve regeneration is slowed after thyroidectomy (in Triton) and rendered normal again by thyroid feeding.⁵

Feeding with thyroid produces an increase in the number of erythrocytes and



FIG. 25.—Toad tadpoles showing acceleration of metamorphosis caused by thyroid feeding. (Gudernatsch.)

A, control; B, effect of 5 days' thyroid feeding; C, effect of 15 days' thyroid feeding.

an alteration in the relative numbers of the different types of leucocytes. Phagocytosis is more active.⁶ The bone marrow undergoes a remarkable change (rabbit). The fat-cells disappear, whilst the myelocytes and erythroblasts undergo rapid proliferation.⁷

Effects of Thyroid Feeding on Tadpoles.—Although thyroid feeding tends to hinder growth, it has a remarkable effect in accelerating the metamorphosis of tadpoles⁸ (fig. 25), even if previously thyroidectomised. A similar effect is got with inorganic iodides,⁹ but not if administered before the appearance of the thyroid or after thyroidectomy. On the other hand, B. M. Allen¹⁰ has

¹ *Journ. Exper. Zool.*, xxii., 1917.

² *Amer. Journ. Physiol.*, lxx., 1923.

³ Romeis, *Arch. f. Entwickl.-Mech.*, xl. and xli., 1915.

⁴ *Journ. Exper. Med.*, xvii., 1913.

⁵ *Monatschr. f. Psych. u. Neurol.*, xxxiv., 1913.

⁶ Marbé, *C. r. soc. biol.*, 1908; Zondek, *Deutsch. med. Wochenschr.*, xlviii., 1922.

⁷ C. and M. Parhon, *C. r. soc. biol.*, lxxi., 1911; Lim, Sarkar, and Brown, *Journ. Path. and Bact.*, xxv., 1922.

⁸ Gudernatsch, *Zentrbl. f. Physiol.*, xxvi., 1912; *Arch. f. Entwickl.-Mech.*, xxxv., 1912; *Amer. Journ. Anat.*, xv., 1913-14; *Anat. Rec.*, xi., 1917.

⁹ Uhlenhuth, *Journ. Gen. Physiol.*, i., 1919; *Biol. Bull.*, xlii., 1922.

¹⁰ *Anat. Rec.*, xiv., 1918; *Journ. Exper. Zool.*, xxiv., 1918.

shown that extirpation of the thyroid in the tadpole retards or altogether prevents metamorphosis, although the animals grow large and their lungs and reproductive organs develop: indeed these thyroidless tadpoles may grow to a much larger size than normal animals, the earliest effects being seen upon the skeleton, which undergoes hypertrophy, although its ossification is retarded.¹ The thymus, spleen, kidney, and brain cease to develop, the gills persist, the fore-limbs do not break through the skin, the intestine remains long.²

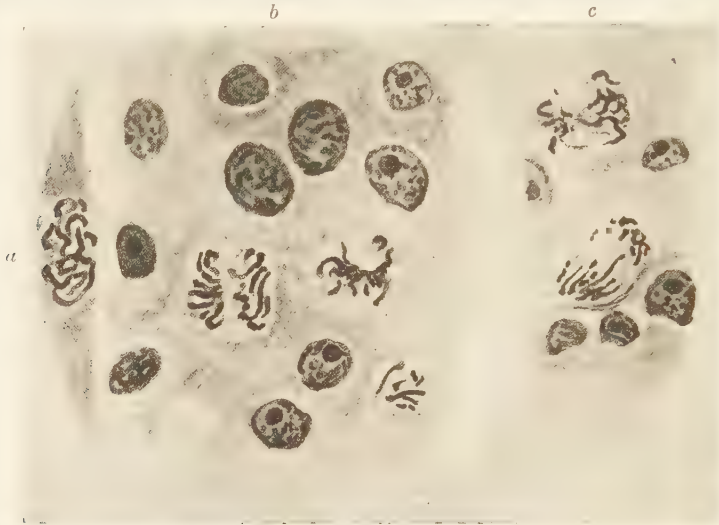


FIG. 26.—Mitoses seen in a tangential section of the gastric mucosa of a thyroid-fed tadpole of *Rana temporaria*. Magnification about 1500 diameters. (R. K. S. Lim.)

a, an involuntary muscle-fibre; *b* and *c*, cells in the deep layer of the mucosa. (All these mitoses were seen in one field of the microscope.)

Note the large size of several of the resting nuclei.

The effect of increased growth may result indirectly from enlargement of the pituitary body.³ Previous destruction of the pituitary does not prevent metamorphosis.⁴ According to W. W. Swingle, free iodine may accelerate the metamorphosis of toad tadpoles even after thyroidectomy,⁵ but it does not influence those of *Salamandra* or *Triton*⁶ nor of the axolotl,⁷ which normally remains throughout life as a large gill-bearing tadpole, but can be caused to metamorphose by thyroid feeding.⁸

¹ G. S. Terry, *Jour. Exper. Zool.*, xxiv., 1918.

² See on this subject, E. R. and M. M. Hoskins, in *Proc. Soc. Exper. Biol.*, xv., 1918 (they performed thyroidectomy in a large number of tadpoles 6 to 8 mm. in length); also in *Endocrinology*, iv., 1920.

³ J. B. Rogers, *Journ. Exper. Zool.*, xxiv., 1918.

⁴ Leo Adler, *Arch. f. Entwickl.-Mech.*, xxxix., 1914. Large amounts of iodine produce metamorphosis in the absence of both thyroid and pituitary (B. M. Allen, *Biol. Bull.*, xxxvi., 1917), *Anat. Rec.*, xv., 1919.

⁵ *Endocrinology*, ii., 1918; *Journ. Exper. Zool.*, xxvii., 1919.

⁶ J. Huxley and L. Hogben, *Proc. Roy. Soc.*, B, xciii., 1922.

⁷ Uhlenhuth, *Journ. Gen. Physiol.*, i., 1919; *Biol. Bull.*, xlii., 1922.

⁸ This was first described by Babak (*Zentrbl. f. Physiol.*, xxvii., 1913) and by Laufberger;

Thyroid-fed tadpoles develop enlarged thymus glands, but their thyroids and pituitaries are smaller than in controls. Thymus feeding causes the opposite effects.¹

The tissues of tadpoles which are induced to undergo premature metamorphosis by thyroid feeding exhibit a very large number of mitoses² (fig. 26). The hydrolysed products of the thyroid have the same effects on the metamorphosis of tadpoles as extracts of the gland.³

The same is the case with the thyroxin of Kendall. Extracts of thyroid made with 95 per cent. alcohol have a marked influence in promoting metamorphosis, whilst extracts of the residue give negative results.⁴

Thyroxin is also effectual in causing metamorphosis of the axolotl, even after thyroidectomy.⁵ Hogben finds that the thyroidectomised axolotl can be made to undergo metamorphosis by injection of extract of anterior lobe of pituitary.⁶ Substances like salicylic acid, which increase metabolism, have also been stated to accelerate the metamorphosis of the axolotl.⁷

W. W. Swingle⁸ got metamorphosis of both thyroidectomised and normal axolotls and of normal frog-tadpoles by intraperitoneal injections of iodo-tyrosine, iodo-serumglobulin, and iodo-casein, but found that bromine compounds had no effect.

Gayda⁹ finds that tadpoles, the metamorphosis of which is accelerated by thyroid feeding, show an increased heat production as compared with controls.

Metamorphosis will proceed in frog or toad tadpoles even if they are kept narcotised for several days with urethane,¹⁰

The metamorphosis of most invertebrates is not influenced by thyroid feeding.¹¹ But A. Vecchi¹² found that thyroid feeding causes a marked abbreviation in the duration of the larval period of Cyclops, and Kunkel states that flesh-fly larvae develop more rapidly when fed on thyroid substance.

later by Jensen (*C. r. soc. biol.*, lxxxiii., 1920), and by Huxley and Hogben (*op. cit.*). Amphibian metamorphosis is always attended by prominence of the eyeballs (exophthalmos). This was noted both for tadpoles and the axolotl by Abderhalden (*Arch. f. d. ges. Physiol.*, clxii., 1915). Accounts of the effects of thyroid feeding on tadpoles are given by Fulton, in *Endocrinology*, v., 1921, by R. K. S. Lim, in *Science Progress*, 1920, and by Hogben, in *Science Progress*, 1921. The effect of iodine is discussed at length by Uhlenhuth in *Biol. Bull.*, March 1922.

¹ R. H. Kahn, *Arch. f. d. ges. Physiol.*, clxiii., 1916.

² R. K. S. Lim, *Quart. Journ. Exper. Physiol.*, xii., 1920. See also Dragoin and Fauré-Fremiet, *C. r. soc. biol.*, lxxv., 1921; Champy, *Arch. de morph.*, 1922; Romeis, *Arch. f. inter. Anat. u. Entw.*, xcviii., 1923.

³ Abderhalden, *Arch. f. d. ges. Physiol.*, 1919. Various other papers on this subject by the same author have appeared in the *Arch. f. d. ges. Physiol.* from 1915 to 1921.

⁴ E. C. Seaman, *Amer. Journ. Physiol.*, liii., 1920.

⁵ C. O. Jensen, *C. r. soc. biol.*, lxxv., 1921.

⁶ Private communication. A commercial preparation was employed.

⁷ L. Kaufmann, *Bull. de l'Acad. des Sci.*, Cracovie, 1918.

⁸ *Biol. Bull.*, xlv., 1923.

⁹ *Arch. d. fisiol.*, xix., 1921.

¹⁰ J. Huxley, *Proc. XIth Intern. Physiol. Congr., Quart. Journ. Exper. Physiol.*, Suppl. vol., 1923.

¹¹ Kahn, *Arch. f. d. ges. Physiol.*, excii., 1921.

¹² *Arch. di fisiol.*, xvii., 1919.

CHAPTER VI

THE THYROID (*continued*)

HYPERTHYROIDISM IN DISEASE

Exophthalmic Goitre.—This affection, first described by Parry (1786), is also associated with the names of Flajani (1802), Graves (1835), and Basedow (1840), all of whom called attention to the chief symptoms.¹ The name *exophthalmic goitre* expresses its most prominent signs (fig. 25).

The disease is usually accompanied by considerable enlargement of the thyroid. The opinion is widely prevalent that the enlargement is accompanied by hypersecretion, which is the direct cause of the symptoms, this opinion being founded on the facts that (1) many of the symptoms of the disease can be produced by administration of thyroid in excess, and (2) the symptoms are for the most part opposite in character to those which are known to be produced by atrophy, removal, or diminution of function of the gland. Thus there is a rapid, powerful, and often irregular action of the heart (tachycardia), with moderately high blood-pressure; nervous and psychical excitement; muscular tremors; a feeling of warmth in the skin—which may, however, be pale—and throbbing of cutaneous vessels, often accompanied by profuse sweating; rapid shallow respirations; markedly increased metabolism (especially nitrogenous), with abnormal appetite and loss of body-fat; a decreased assimilatory power for carbohydrates, so that alimentary glycosuria is readily obtained; an anxious, restless expression; prominence of the eyeballs and wide palpebral aperture. The enlarged gland pulsates and gives a murmur on auscultation. Dyspnoea is common. Watery diarrhoea is not infrequent. Basal metabolism is always markedly increased, and is almost pathognomonic of the disease.

Exophthalmic goitre is far more common in the female than in the male (as 4·6 to 1), a fact which may be related to the enlargement of the gland, which usually occurs in the female at puberty and during pregnancy. It is generally associated with a persistent or enlarged thymus,² which has by some authors been credited with the production of certain of the symptoms of the disease.

¹ Parry collected eight cases and correctly described the principal symptoms. Flajani described two cases of goitre with cardiac palpitation. Graves and Basedow described three and four cases respectively. Graves looked upon the pulsating tumour of the thyroid as caused by the augmented action of the heart, which he regarded as the primary affection. Basedow considered both symptoms to be secondary to a scrofulous condition (dyscrasia) of the blood. It was Moebius (*Centrbl. f. Nervenl.*, 1887; also *Nothnagel's Handbuch*, 1896) who insisted upon the condition of the thyroid being the primary affection, and who pointed out the striking contrast between exophthalmic goitre on the one hand, and myxoedema, cachexia thyreopriva, and endemic goitre on the other (see p. 58).

² W. S. Halsted, *Harvey Lectures*, 1913-14.

That it plays some part in producing the symptoms would seem probable if it is true that better results are obtained in the surgical treatment of that disease if the thymus is removed along with a large part of the thyroid¹ than if the thyroid alone is operated on.

E. Bircher claims to have produced the symptoms of exophthalmic goitre in dogs by implanting normal human thymus into the peritoneum. But in view of the difficulty of getting heteroplastic grafts to take, these experiments need confirmation before they can be accepted.²

About 13·5 per cent. of cases have polyuria without sugar. Only 2 per cent. have permanent glycosuria, although alimentary glycosuria is not uncommon. A certain degree of hyperglycæmia is frequently found.³ Albuminuria is present in about 11 per cent. The nervous excitability which accompanies hyperthyroidism is quite different from that of tetania parathyreopriva. Galvanic excitability of the peripheral nerves and muscles is practically normal in hyperthyroidism, whereas it is much increased both in sporadic tetany and in tetania parathyreopriva. Moreover, between the fits in tetany there is evidence of general nervous depression.

Cases in which only one eye shows exophthalmos have not infrequently been noted. In these the goitre and the muscular tremors are usually confined to the same side.

The cause of the protrusio bulbi is somewhat uncertain. It is probably due to a spastic contraction of plain muscle in the orbit caused by hyperexcitation through the sympathetic: this would also account for acceleration of the heart.⁴

Three of the symptoms above enumerated—tachycardia, muscular tremors, and increased metabolism—are observed in commencing hyperthyroidism even before enlargement of the thyroid can be detected. The exophthalmos is usually developed late, and may be absent.

Dilatation of the pupil is not a constant sign, although not uncommon. Loewi found that adrenaline dropped into the eye dilates the pupil, which is not the case in the normal subject.

The increase of metabolism was first observed by F. Müller.⁵ The basal metabolism, as measured by oxygen consumption and carbonic acid excretion,



FIG. 27.—Case of exophthalmic goitre.
(Byrom Bramwell.)

¹ H. Harberer, *Mitteil. a. d. Grenzgeb. d. Med. u. Chir.*, xxxii., 1922.

² *Centrbl. f. Chir.*, xxxix., 1912, and *Berlin. klin. Wochenschr.*, lxxxix., 1914.

³ A. E. Garrod, *Lancet*, i., 1912.

⁴ G. R. Murray believes the protrusio bulbi to be caused by accumulation of orbital fat. Basedow's original paper is entitled "Exophthalmus durch Hypertrophie des Zellgewebes in der Augenhöhle" (*Woch. f. d. ges. Heilk.*, 1840).

⁵ *Arch. f. klin. Med.*, 1893.

may be increased by more than 50 per cent. in severe cases. It may be used as a measure of the progress of the disease. The warmth of the skin and sweating serve to assist in eliminating the excess of heat produced. And although a large amount of food may be taken, the body loses in weight, often very considerably.¹

G. R. Murray² classifies the condition of hyperthyroidism in the human subject in three grades, viz. (1) simple hyperthyroidism, shown by increase of basal metabolism ; (2) toxic goitre, in which there is enlargement of the gland,

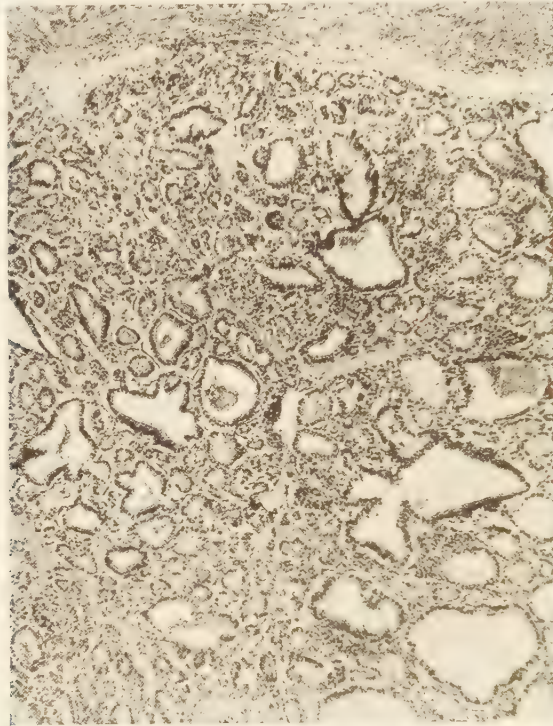


FIG. 28.—Section of thyroid from a case of exophthalmic goitre. Magnified 75 diameters. (Photograph.)

increase of basal metabolism, and increased rapidity of pulse with a tendency to nerve excitation ; and (3) exophthalmic goitre, in which all the ordinary symptoms of hyperthyroidism are seen in an accentuated form, and with them protuberance of the eyeballs.

Complete rest in bed ; treatment of the thyroid by X-rays ; and the administration of arsenic and bromides are recommended by Murray. But if the symptoms

¹ On the basal metabolic rate in exophthalmic goitre, see Sandiford, in *Endocrinology*, iv., 1920 ; and J. Meakins and H. W. Davies, in *Edin. Med. Journ.*, 1922.

² *Brit. Med. Journ.*, 1922. Earlier papers by Murray on this subject are to be found in the *Lancet*, ii., 1905, and the *Brit. Med. Journ.*, ii., 1916. See also, H. Mackenzie, in Allbutt's *System of Medicine*, 1908, and the *Lancet*, ii., 1916 ; and W. Edmunds, *Exophthalmic Goitre*, London, 1922.

are severe, removal of a considerable part of the gland is the only remedy which is likely to be of material benefit.¹

The toxic symptoms of exophthalmic goitre generally reach their maximum within twelve months, after which there may be a return to normal. Or the symptoms may persist with fluctuations for from two to four years. If prolonged, there are serious degenerative changes in the nervous system, heart, blood-vessels, and kidneys.²

The histological appearances (figs. 28 and 29) are conformable with the theory of a hypersecretion. The gland is greatly enlarged, and the individual vesicles are irregular and tend to run together. The interstitial tissue is increased in amount and assumes a lymphoid appearance, sometimes with

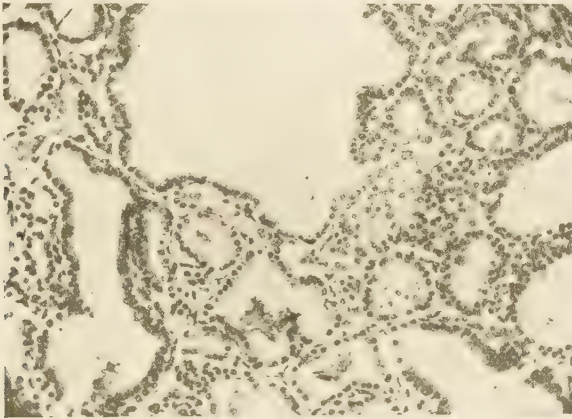


FIG. 29.—Part of the same section, magnified 200 diameters. Notice the irregularity in size and shape of the vesicles, and the fact that they are mostly empty of coagulated colloid.

characteristic germinal centres. The follicle wall tends to grow into the interior of the conjoined follicles in the form of projections, thus increasing the surface for secretion and giving the cavities a still more irregular aspect. In some parts the follicles are smaller than usual, and may even disappear. The cells lining the follicles tend to acquire a columnar form and show an increase in the number of mitochondria:³ in later stages the cells may undergo degeneration and become free within the follicles. The contents of the follicles are more fluid than in the normal thyroid, and in sections show little or no coagulated colloid.⁴

¹ E. and M. Mellanby, who find that the vitamin which occurs in butter accentuates the symptoms of hyperthyroidism, recommend that it be excluded from the diet of patients with exophthalmic goitre. *Journ. Physiol.*, iv., 1921, *Proc. Physiol. Soc.*

² For the after-history of a large number of cases of exophthalmic goitre, see Hale-White, *Quart. Journ. Med.*, iv., 1910.

³ Goetsch, *Johns Hopkins Hosp. Bull.*, xxvii., 1916.

⁴ See on the subject of the appearances of the thyroid in exophthalmic goitre, W. G. Greenfield, Bradshaw Lecture, *Brit. Med. Journ.*, ii., 1893; D. Marine and C. H. Lenhart, *Arch. intern. Med.*, vii. and viii., 1911; and G. Roussy and J. Clunet, *Ann. d. méd.*, i., 1914.

Direct proof of the hypersecretion of the thyroid was thought to be furnished by the experiments of Reid Hunt, who found that the blood of a person afflicted with exophthalmic goitre increases the resistance of mice to the poisonous effects of aceto-nitrile (CH_3CN); an effect he had previously found to result from injection of thyroid extract.¹ Miura² states that thyroxin has the same effect as thyroid extract, but Reid Hunt has shown that, compared with its iodine content, it is less active than thyroid. This has also been found by Cameron and Carmichael for the respective effects on growth (see p. 46).

Another test recommended for hyperthyroidism is the increased effect produced by adrenaline owing to the hypersensitising of the sympathetic endings by excess of thyroid in the blood. After subcutaneous injection of thyroid extract or of iodo-thyroglobulin adrenaline is said to have a far more prolonged effect upon blood-pressure than normally.³ Stimulation of the

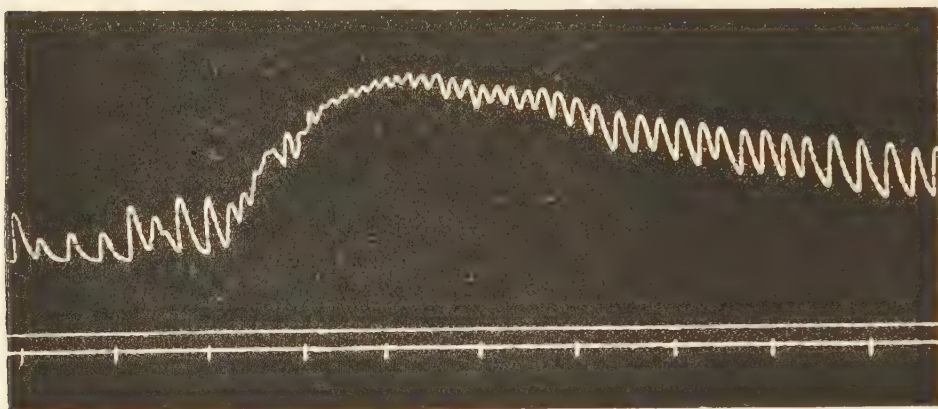


FIG. 30.—Effect upon an isolated strip of intestinal muscle (cat ileum) of the addition to the Ringer solution in which it is suspended of a minute amount of normal human serum. Time in minutes.

cervical sympathetic is also said to increase the sensitiveness of the sympathetic endings to adrenaline by causing an excess of thyroid secretion.⁴ But in view of the experiments of Lieb and Hyman, and of Dryerre (see p. 44), the statement that thyroid increases the sensitiveness of sympathetic endings must be received with caution.

In exophthalmic goitre the blanching of the skin caused by hypodermic injection of adrenaline is said to last much longer than in a normal subject (see p. 100).⁵ Further, the blood or serum of patients suffering from this disease

¹ *Journ. Biol. Chem.*, i., 1905; *Journ. Amer. Med. Assoc.*, xlix., 1907; Hunt and Seidell, Treasury Depart., Washington, Hygienic Lab., *Bull.*, 47, 1909; *Journ. Pharm. and Exper. Therap.*, ii., 1910; Hunt, *Amer. Journ. Physiol.*, lxiii., 1923. The subject is fully discussed in this paper and the literature given.

² *Journ. Lab. and Clin. Med.*, vii., 1922.

³ Asher and von Rodt, *Zentrbl. f. Physiol.*, xxvi., 1912; Oswald, *Zentrbl. f. Physiol.*, xxx., 1915.

⁴ Levy, *Amer. Journ. Physiol.*, xli., 1916.

⁵ E. Goetsch, *New York State Journ. Med.*, 1918 to 1921.

excites the contraction of a suspended slip of intestinal muscle to a far greater extent than the same amount of blood or serum from normal persons (compare figs. 30 and 31).¹

Since an increased effect is also produced by extract of thyroid, the fact might be taken as a proof that the blood in exophthalmic goitre contains an excess of thyroid secretion.² But neither the aceto-nitrile test nor the intestinal muscle test are diagnostic of thyroid secretion: indeed thyroid extract is by no means a powerful stimulant of intestinal muscle, and the specific autacoid of thyroid—thyroxin—produces no effect on the intestinal slip,³ and, expressed quantitatively in terms of iodine content, less effect in

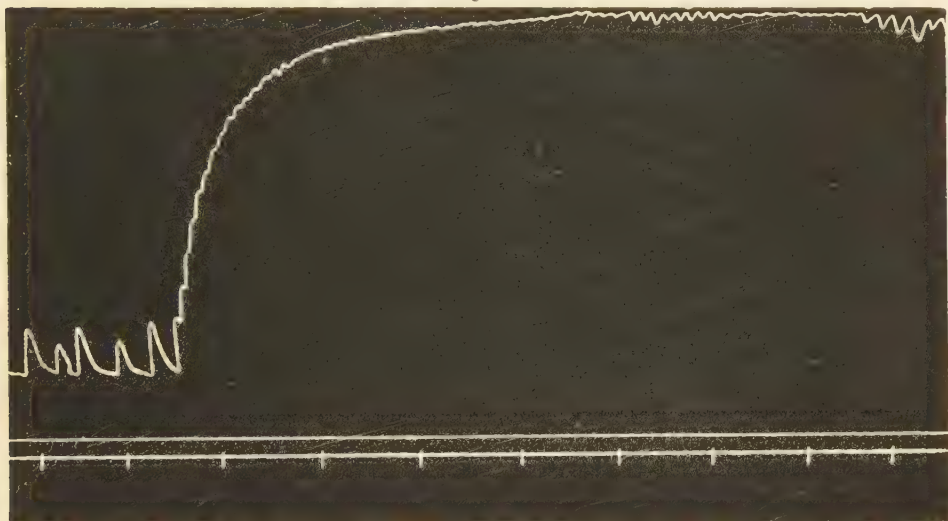


FIG. 31.—Effect of a similar amount of serum from a case of exophthalmic goitre on the same piece of muscle as in fig. 30.

protecting mice against aceto-nitrile than thyroid gland itself.⁴ The excitation therefore cannot be due to thyroxin, but must be due to some other material, which may or may not be furnished by the thyroid. Further, the blood in some other affections (*e.g.* nephritis) and that of thyroidectomised animals is found to contain a substance which is protective to mice against aceto-nitrile:⁵ in the latter case there can certainly not be any thyroid derivative. The test which is most specific for the thyroid autacoid, *viz.* the acceleration of the metamorphosis of tadpoles, gives negative results both for normal and

¹ E. Sharpey-Schafer, *Quart. Journ. Exper. Physiol.*, xiii., 1923.

² The favourable results which ensue in many cases from surgical removal of a large portion of the hypertrophied gland or ligature of some of its vessels also point in the direction of an increase of secretion. For the history of this operation, see W. S. Halsted, *Johns Hopkins Hosp. Bull.*, xix., 1920. This article contains an extensive bibliography.

³ F. S. Hammett, *Amer. Journ. Physiol.*, lvi., 1921.

⁴ Reid Hunt, *Amer. Journ. Physiol.*, lxxiii., 1923.

⁵ Trendelenburg, *Biochem. Zeitschr.*, xxix., 1910.

for exophthalmic blood.¹ Since thyroxin produces acceleration of metamorphosis, this result suggests that thyroxin is not present in appreciable amount in the blood even in exophthalmic goitre, although it does not negative the assumption that there is increased activity of the gland and increased secretion, which may, however, be of an altered character.²

Some observers have stated that injection of blood-serum from cases of exophthalmic goitre produces effects in animals similar to the symptoms of that disease in man. But Gley and Cleret³ find that, although in dogs small doses of extract from an exophthalmic goitre may cause increased rate of heart-beat and some rise of blood-pressure, this is soon followed by the opposite condition. They therefore hold that the symptoms are produced not by excess of normal thyroid secretion circulating in the blood, but as the result of the production of a perverted secretion (dysthyroidism).⁴

Many of the symptoms of exophthalmic goitre are very similar to those caused by hypersecretion of adrenaline, *e.g.* the protrusion of the eyeballs, with widened palpebral aperture, the acceleration of the pulse, and the relatively high blood-pressure. It is, however, not possible by any known physiological test to prove the presence of adrenaline in the blood in this disease—indeed, as we have seen, an intestinal strip, so far from being inhibited by exophthalmic blood, has its contractions increased both in number and extent; more in fact than by normal blood. Using the rabbit's uterus as a test, A. Fraenkel⁵ states that he was able to show 4 to 8 times more adrenaline in the blood in cases of exophthalmic goitre than in normal blood. Yet this amount produced no constriction of blood-vessels, and it is entirely contrary to the results of Gottlieb,⁶ of Stewart,⁷ and to those I have myself obtained⁸ with the intestinal slip. The above symptoms of exophthalmic goitre cannot therefore be ascribed to free adrenaline, but must be due to an increased excitability of the sympathetic, the cause of which is at present undetermined.⁹ The fact that

¹ E. Sharpey-Schafer, *op. cit.* See also Abderhalden and Schoffmann (*Arch. f. d. ges. Physiol.*, xciv., 1922), who got no result from goitrous thyroids either endemic or exophthalmic. Rogoff (*Journ. Pharm. and Exper. Therap.*, xii., 1918) states that he obtained acceleration of metamorphosis in tadpoles by feeding them with blood from the thyroid veins of the dog, but his figures are not convincing. In a later paper, with Goldblatt (*ibid.*, xvii., 1921), Rogoff failed to get any result on tadpoles fed with blood taken from the thyroid veins during operations for exophthalmic goitre in man.

² See R. G. Hoskins, in *Endocrinology*, ii., 1918; N. W. Janney, in *Archives of Internal Medicine*, xxii., 1918; and C. P. Howard, in the article, "Clinical Syndromes due to Thyroid Disease," in Barker's *Endocrinology and Metabolism*, 1922. For other suggested tests of the presence of thyroid secretion in blood, see the *Prescriber*, xvi., 1922 (October number).

³ *Journ. de physiol.*, xiii., 1911.

⁴ See on this subject, H. Klose, *Arch. f. klin. Chir.*, xciv., 1911.

⁵ *Arch. f. exper. Path. u. Pharm.*, lx., 1909.

⁶ *Deutsch. Med. Woch.*, 1911.

⁷ *Journ. Exper. Med.*, xv., 1922.

⁸ *Quart. Journ. Exper. Physiol.*, xiii., 1923.

⁹ L. B. Wilson and Durante (*Journ. Med. Res.*, 1916) found degenerative changes in the cells of the superior cervical ganglia in 16 patients who had died from exophthalmic goitre. These changes were absent in individuals who had died from other diseases. Wilson claims to have produced exophthalmic goitre in goats by infecting the superior cervical ganglion with bacteria (*Amer. Journ. Med. Sci.*, 1918).

some cases of exophthalmic goitre are found to benefit by administration of adrenaline¹ is an indication that the above symptoms are not produced by an excess of that autacoid.²

According to D. J. Harries,³ exophthalmic goitre is associated with excessive absorption of tryptophane from the intestine, caused by absence of indol-producing bacteria. He finds indican absent from the urine in this affection.

The thyroid from cases of exophthalmic goitre contains as a rule less iodine in proportion than normal thyroid, and much less than the tumours of endemic goitre. But the secretion is probably formed rapidly in exophthalmic goitre and passed into the blood as soon as it is formed—whereas in endemic goitre the formation is probably slow, and its passage into the blood interfered with.

Although most of the symptoms of exophthalmic goitre are directly contrary to those of endemic goitre, others are common to both conditions. This is especially manifested in the frequent occurrence of affections of the skin, hair, and nails, and of amenorrhœa in females. In both affections the blood picture shows an increase in the number of the large mononuclear and of the oxyphil leucocytes.⁴

The table on p. 58 shows the chief differences of the symptoms exhibited in myxœdema (and endemic goitre) and in exophthalmic goitre respectively.

THYROID MEDICATION

Thyroid medication has been found beneficial not only in endemic goitre and myxœdema⁵ and the mental disorders accompanying them, but in a few cases of climacteric insanity and in some cases of tetany. It has been recommended for certain forms of insanity and in epilepsy.⁶ It is said to be of use in the treatment of dry, chronic eczema; and chronic psoriasis often disappears with large doses—but may return after discontinuance.⁷ Although contra-indicated in the acute stage of exophthalmic goitre, thyroid is stated to be sometimes useful after this affection has become chronic.⁸ Cases of acromegaly are described as having improved under thyroid treatment.⁹ It has been administered successfully to backward children, the “backwardness” being probably associated with thyroid deficiency. Enlarged tonsils and adenoids are said to be occasionally associated with thyroid inadequacy, thyroid medication having been successful in effecting improvement of these conditions in some cases.¹⁰ It has also been

¹ G. A. Gibson, *Lancet*, ii., 1912.

² A case of exophthalmic goitre with rapid improvement following on oral administration of fresh ox-suprarenal (containing chiefly cortex) is recorded by Shapiro and Marine in *Endocrinology*, v., 1921. See also Warren, *Lancet*, 1913 (adrenaline), and Obregia, *C. r. soc. biol.*, lxxxiv., 1921, who finds the whole suprarenal acts better than adrenaline.

³ *Brit. Med. Journ.*, i., 1923, p. 553.

⁴ For an important discussion on the treatment of exophthalmic goitre, see *Proc. Roy. Soc. Med. (Clinical Section)*, xlv., 1922.

⁵ W. Hale-White, *Materia Medica*, London, 1915.

⁶ C. C. Easterbrook, *Organo-therapeutics in Mental Diseases*, 1900.

⁷ G. R. Murray, *Brit. Med. Journ.*, ii., 1909; *Lancet*, 1913, pp. 204 and 382.

⁸ H. Mackenzie, *Brit. Med. Journ.*, 1905, ii., p. 1081; Dreschfeld, *Med. Chron.*, 1906.

⁹ G. A. Gibson, *Brit. Med. Journ.*, ii., 1904, p. 1381.

¹⁰ Waller, *Brit. Dental Journ.*, Jan. 1912; J. G. Cobb, *New York Med. Journ.*, 1922.

MYXŒDEMA AND ENDEMIC GOITRE

EXOPHTHALMIC GOITRE

Thyroid Gland

Atrophied or enlarged. If enlarged, well defined and not pulsatile. Vesicles distended by colloid. Cells flattened. Gland functionally inert.	Always enlarged. Ill defined. Pulsatile and hyperæmic. Vesicles irregular ; containing no colloid. Cells prominent. Gland functionally over-active.
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Heart

Beats—slow, weak, regular.	Rapid, forcible, often irregular.
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Blood-vessels

Contracted. Vasomotor nervous system relatively inexcitable.	Dilated. Vasomotor nervous system readily excitable.
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Integument

Pallid, cold, thickened, surface dry.	Flushed, warm, delicate, surface moist.
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Respirations

Slow, often laboured.	Rapid, often shallow.
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Alimentary Canal

Appetite diminished. Secretions diminished. Tendency to constipation.	Appetite increased. Secretions increased. Tendency to diarrhœa.
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Nitrogenous and Basal Metabolism

Diminished.	Increased.
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Toleration for Carbohydrates

Increased.	Diminished.
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Body-weight

Tendency to increase.	Tendency to decrease.
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Expression

Apathetic, with eyes half shut.	Excited, anxious, with eyes widely opened and prominent.
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Nervous System

Intelligence diminished. Tendency to somnolence. Diminution of reflex excitability.	No diminution of intelligence. Psychological hyperexcitability (often hallucinations). Tendency to insomnia. Increase of reflex excitability.
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Effect of administering Thyroid

Amelioration of symptoms.	Exacerbation of symptoms.
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recommended for nocturnal enuresis.¹ Besides its administration for obesity—in which it doubtless acts by provoking increased metabolism, especially of fats—thyroid has been used successfully in cases of adiposis dolorosa.² It is said to promote union in cases of delayed junction of fractured bones. Halsey has given it in rheumatism, both articular and muscular, in doses of 0.5 to 2 grains per diem, with distinct benefit.³

In all cases care should be taken in its administration—beginning with amounts of not more than 0.06 g. (1 grain) a day, and seldom or never exceeding 1 gram of dry material. Marked acceleration of the pulse is one of the first indications of the supervention of hyperthyroidism; if this occurs the treatment should be arrested. For, as the experiments of Herring have shown, continued administration may have serious effects upon the heart. When a single large dose of thyroid is given the maximum result may not be reached for several days, and the effect may last as long as three weeks.⁴

The affections which are associated with diminution of thyroid secretion in man and animals are discussed at length by Horsley⁵ and by Léopold-Levi and de Rothschild.⁶

Included in these are various affections of the skin, hair, and nails, rheumatic affections of the joints, derangement of the nervous system, and certain forms of infantilism: the beneficial result of thyroid medication being in some cases the chief evidence for their connexion with hypothyroidism.

The changes which can often be seen in the cells of the central nervous system in the insane are similar to those produced by defects of thyroid secretion.⁷

Liddell and Sutherland Simpson find that the muscular activity of sheep deprived of thyroids is increased by administration of thyroxin or thyroid extract—not by sodium iodide.⁸

¹ L. Williams, *Med. Press*, 1909, p. 451.

² Hutchison, *Medical Annual*, 1902.

³ Article, "Organotherapy," in Barker's *Endocrinology and Metabolism*, 1922.

⁴ T. Stephenson, *Prescriber*, xvi., 1922.

⁵ *Lancet*, 1886.

⁶ *Études sur la physiopathologie du corps thyroïde* . . ., Paris, 1908 and 1911.

⁷ Kojima, *Proc. Roy. Soc. Med.*, viii., 1915.

⁸ *Proc. Soc. Exper. Biol. and Med.*, xx., 1922.

CHAPTER VII

THE THYROID (*continued*)

INTERACTION OF THE THYROID WITH OTHER ORGANS

With the Generative Organs.—The important influence exerted by the thyroid secretion on nutrition generally is no doubt responsible for the fact that hardly any organ in the body remains unaffected as a result of its complete removal or atrophy, or of its administration. But the secreting organs with which it may be regarded as being more especially associated are few. Among them are the generative glands. In the female the thyroid becomes enlarged at puberty, during the menses, and during pregnancy. In the young thyroidectomised subject the generative glands are only slowly or imperfectly developed, the resulting condition being characteristically one of sexual infantilism. In the adult animal (dog) Alquier and Theuveny¹ found diminished activity so far as production of spermatozoa is concerned, but less distinct evidence of change in the ovary; although the animals appear to come on incompletely in heat and to conceive rarely. On the other hand, if the ovaries are removed the thyroid tends to become enlarged. According to Gudernatsch,² thyroid, whether administered to the male or the female, has a tendency to prevent fertilisation; and given to pregnant females, to produce abortion. Torrey and Horning³ state that cockerels fed with thyroid assume hen plumage.

With the Liver and Pancreas. Effects of a specific character are produced upon liver glycogen. As already stated (p. 45), Krause and Cramer found that in the cat and rat, fed with thyroid, glycogen disappears from the liver; but there is no glycosuria, the sugar having been conveyed to the tissues and oxidised. Marie Parhon obtained a similar result with the rabbit.⁴ The thyroid feeding tends, as we have seen, to diminish the limit for the assimilation of sugar. This may be due to an increase in the secretion of adrenaline or a direct inhibitory effect on the internal secretion of the pancreas.

After thyroidectomy the assimilation limit for sugar is markedly raised; and according to some observers adrenaline-glycosuria is greatly diminished or fails to show itself. This statement is, however, contradicted by Underhill.⁵ If the parathyroids are included in the removal, the assimilation limit for sugar is lowered, and adrenaline produces a stronger glycosuria than in the normal

¹ *C. r. soc. biol.*, lxiv., 1908, and lxvi., 1909.

² *Amer. Journ. Physiol.*, xxxvi., 1915.

³ *Proc. Soc. Exper. Biol. and Med.*, xix., 1922.

⁴ *Journ. de physiol.*, xv., 1913.

⁵ *Amer. Journ. Physiol.*, xxvii., 1911.

animal. The influence of the thyroids and parathyroids is therefore antagonistic in this as in some other respects. It is stated that if a dog deprived of pancreas and exhibiting glycosuria is thyroidectomised, the sugar disappears from the urine. It is also affirmed that extirpation of the pancreas has the effect of increasing the amount of colloid in the thyroid vesicles, and that thyroidectomy causes a marked increase in the amount of islet tissue in the pancreas. But these latter statements are difficult of acceptance on account of the differences which are normally present, both in amount of colloid in the thyroid and in number of islets in the pancreas. If substantiated they would show a direct correlation between the thyroid and the pancreas, the internal

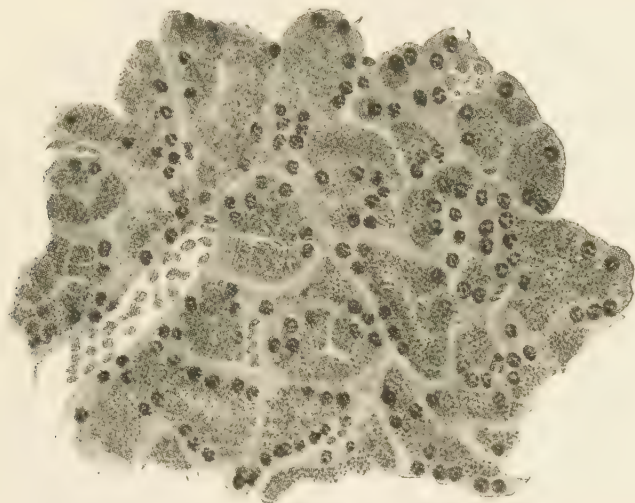


FIG. 32.—Section of pancreas of normal adult male rat, stained by Muir's method. Magnified 400 diameters. (M. Kojima.)

Note the rather small, darkly stained nuclei, and the numerous zymogen granules.

secretion of the thyroid being restrained by that of the pancreas and the internal secretion of the pancreas by that of the thyroid, so that when either gland is extirpated the internal secretion of the other either becomes more active or increased in amount.¹ There is evidence of abundant cell-multiplication (numerous mitoses) in the pancreas of rats fed with large doses of thyroid (fig. 33), although the normal pancreas never exhibits mitoses (fig. 32). There is also a diminution in the number of zymogen granules in the alveolar cells of the thyroid-fed animal: the islets themselves appear unaffected. Iodides have a similar effect, but not in thyroidectomised animals, although in these thyroid produces the reaction.²

With the Suprarenal Capsules.—Thyroid secretion has been said to increase

¹ Cf. Lorand, *C. r. soc. biol.*, lvi., 1904; Eppinger, Falta and Rudinger, *Zentrbl. f. klin. Med.*, 1908; W. G. McCallum, *Johns Hopkins Hosp. Bull.*, xx., 1909; Friedmann and Gottesmann, *Proc. Soc. Exper. Biol.*, xviii., 1921, and xix., 1922.

² M. Kojima, *Quart. Journ. Exper. Physiol.*, xii., 1920.

the activity of all tissues supplied by the sympathetic, and therefore indirectly to increase the effects of adrenaline (see p. 43). Various observers have thought, employing physiological tests, that adrenaline is passed into the blood in larger amount after administration of thyroid extract. But if this increase occurs at all, the effect seems not to be specific for thyroid, since it may be obtained with other tissue extracts, especially liver.¹ On the other hand, when the thyroid is extirpated the activity of the secretion of the suprarenals is diminished, and the phenomena which are normally produced by

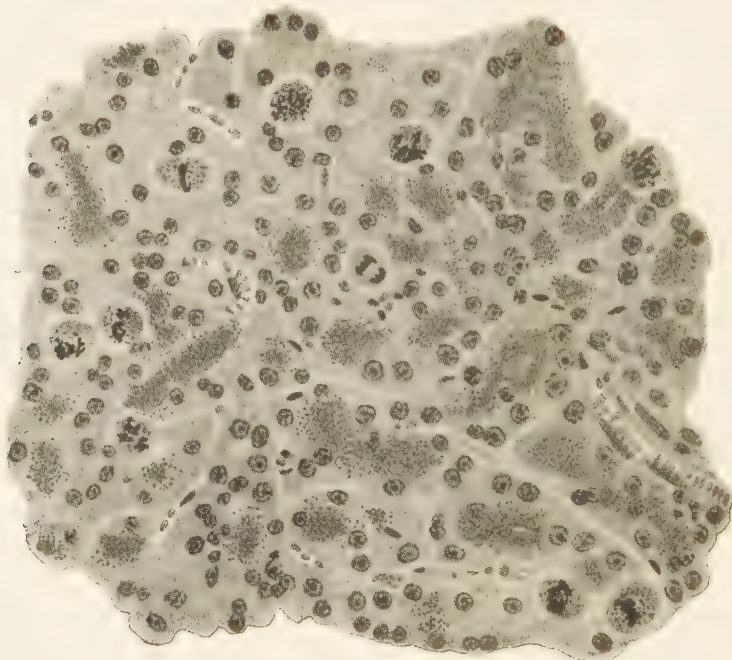


FIG. 33.—Section of pancreas of adult male rat, fed during 7 days before being killed with addition of 1.0 gm. dried ox-thyroid to its ordinary daily food. Stained by Muir's method. Magnified 400 diameters. (M. Kojima.)

Notice the numerous mitoses, the relatively large nuclei, and the comparatively scanty amount of zymogen.

sympathetic stipulation are similarly affected. With hyperthyrosis, such as occurs in intense thyroid feeding, some of the symptoms resemble those caused by adrenaline. But others are different, and indeed the opposite of those produced by adrenaline. And whereas some observers have obtained effects which lead them to believe there is an excess of adrenaline in the blood in hyperthyrosis,² others have failed to get such results. These effects, even if

¹ Gley and Quinquaud, *Arch. intern. de physiol.*, xiv., 1914. Lieb and Hyman (see p. 44) have shown that there is always, in pithed cats, a progressively increasing response to the same dose of adrenaline which has not been taken into account by prior workers. The cause of this "variable" has not been determined.

² A. Fraenkel, *Arch. f. exper. Path. u. Pharm.*, lx., 1909. Fraenkel used the contraction of the cornu uteri of the rabbit as a test object, but it is doubtful if the increased contraction he obtained was due to adrenaline.

present, may be susceptible of another explanation. Nevertheless it is incontestable that thyroid feeding and thyroid deprivation affect the size of the suprarenal capsules. Both Hoskins and Herring note as one of the symptoms of thyroid feeding in rats an increase in size of the suprarenal capsules, and this has been confirmed by Cameron and Carmichael, Cameron and Sedzick, and (for rabbits) by Squier and Grabfield.¹

Herring² has investigated the amount of adrenaline in the suprarenals of animals (cats, rabbits, and rats) both normal and after being (*a*) thyroid fed and (*b*) thyro-parathyroidectomised. In the rabbit he found little if any permanent effect on the amount of adrenaline as the result of thyroidectomy alone (which in this animal is normally borne without the production of any adverse symptoms). In cats which exhibited tetany and muscular weakness the amount of adrenaline was greatly reduced, while in cats fed with ox-thyroid it was considerably increased (fig. 34). The relative amounts were tested both by Elliott's method (injection into the jugular vein of a pithed cat of a definite amount of the extract of both suprarenals³) and by Folin's colorimetric method.⁴ The increase is correlated with a general enlargement of the organs, which involves both cortex and medulla; but especially the cortex, so that the actual percentage amount of adrenaline is slightly decreased. Herring found that in the female rat the suprarenals are much larger proportionately than in the male, and contain more than twice as much adrenaline. The proportion is increased during pregnancy. The actual amount is not so much increased by thyroid feeding in the female as in the male: the percentage amount is, in fact, diminished. The administration of adrenaline excites the thyroid to activity, probably acting through its sympathetic nerve-supply.⁵ Black, Hupper, and Rogers⁶ state that in dogs fed for some time with extracts of the whole suprarenal the iodine content of the thyroid materially increases. Adrenaline alone had little or no effect.

The reputed effect of thyroid extract in promoting the action of adrenaline has been just referred to. Many observers confidently state that such an effect is readily obtained. Thus Eiger⁷ got augmentation of the action of adrenaline on the perfused vessels of the frog as the result of addition of thyroid extract, and a similar effect from the addition of plasma from the inferior thyroid vein (of the dog) and from thyroid-fed rats: also with serum from cases of exophthalmic goitre.⁸ We have already seen that the effects of the serum from exophthalmic goitre upon an intestinal muscular slip do not indicate any increase of adrenaline. Santesson⁹ states that feeding with thyroid increases the sensitiveness of animals to the vascular effects of adrenaline. H. B. Richardson¹⁰ finds that the action of

¹ *Endocrinology*, vi., 1922.

² *Quart. Journ. Exper. Physiol.*, ix., 1916; xi., 1917 (two papers); xii., 1919. The whole subject is discussed at length by Herring in *Endocrinology*, iv., 1920.

³ *Journ. Physiol.*, xlv., 1912.

⁴ Folin, Cannon, and Denis, *Journ. Biol. Chem.*, xiii., 1913.

⁵ G. W. Crile, *New York Med. Journ.*, 1921.

⁶ *Amer. Journ. Physiol.*, lix., 1922.

⁷ *Zeitschr. f. Biol.*, lxvii., 1917.

⁸ This had previously been stated to be the case by Asher and von Rodt (*Zentrbl. f. Physiol.*, xxvi., 1912).

⁹ *Skand. Arch. f. Physiol.*, xxxvii., 1919.

¹⁰ *Zeitschr. f. Biol.*, lxvii., 1917.

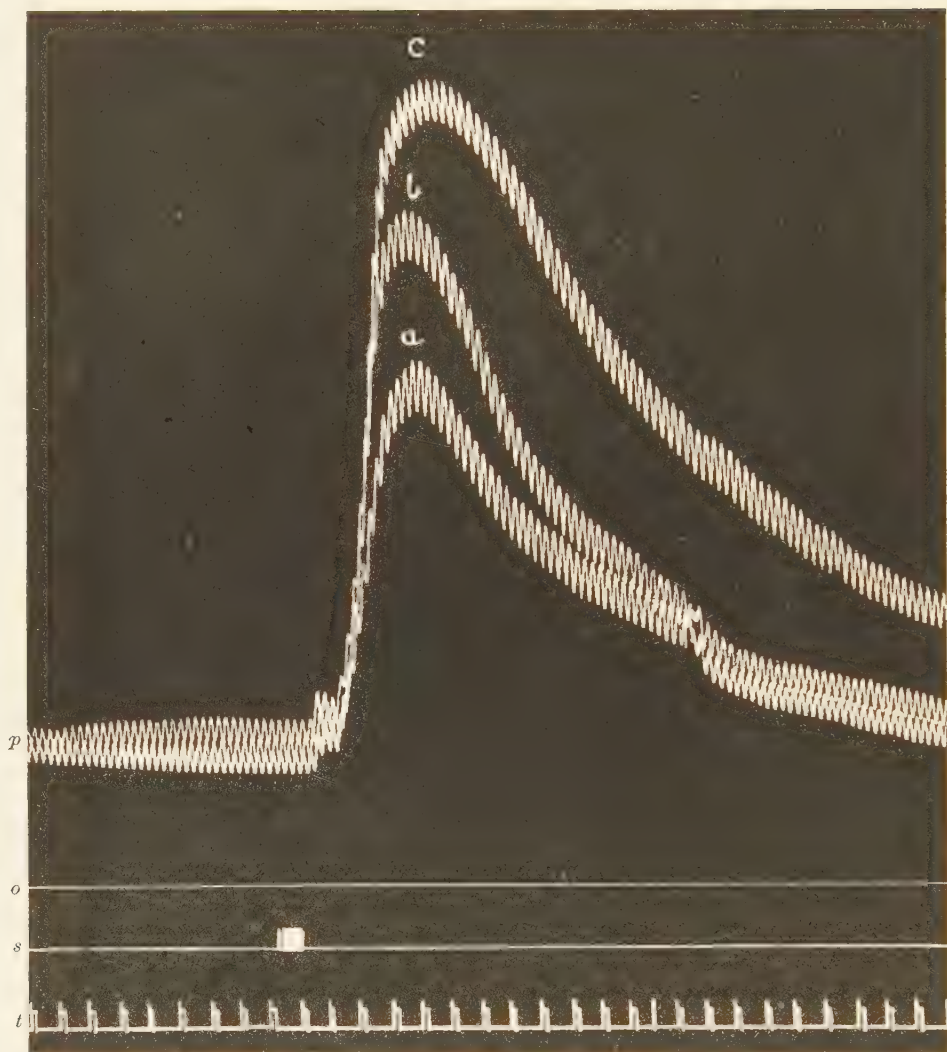


FIG. 34.—Three superposed tracings illustrating the relative amounts of adrenaline in the suprarenals of a thyroidectomised, a normal, and a thyroid-fed cat. (Herring.)

Tracing *a* represents the rise of blood-pressure in the carotid of a pithed cat following upon the injection into the jugular vein of 2 c.c. Ringer's solution containing $\frac{1}{2}$ th of the extract of the suprarenals of a cat (A) killed 9 days after removal of the thyro-parathyroid apparatus. The animal's weight at death was 2835 g.

Tracing *b* is a similar experiment on the same pithed cat, but the extract was made from the suprarenals of a normal cat (B) weighing 2835 g.

Tracing *c* is a similar experiment on the same pithed cat, but the extract was made from a cat (C) which had been fed during 21 days with raw ox-thyroid in addition to the ordinary diet of bread and milk. Its weight when killed was 2270 g.; the original weight having been 3285 g.

The animals were all males. The weights of the suprarenals in A and C were the same; that of B was rather less.

p., blood-pressure curve; *o.*, abscissa; *s.*, signal.

adrenaline on the perfused heart of the rabbit is markedly strengthened by previous or simultaneous perfusion with thyroid extract.¹ Eppinger, Falta, and Rudinger² state that adrenaline-glycosuria does not occur after thyroidectomy, and Grey and de Sautelle³ got diminution of sugar: but Underhill and Hilditch⁴ obtained glycosuria in dogs deprived of thyroid and retaining at least two parathyroids. Kamo⁵ also states that adrenaline causes less glycosuria in thyroidectomised than in normal dogs, and is non-toxic for the former. On the other hand, he finds it highly toxic for parathyroidectomised animals.

W. Cramer⁶ finds that the drug β -tetrahydronaphthylamine causes intense stimulation both of the thyroid and suprarenal capsules. The effect is the same as a prolonged excitation of the whole sympathetic system. There is mobilisation of the liver glycogen, and the temperature rises in the same way as in heat-stroke, a fatal hyperpyrexia being produced unless remedial measures (artificial cooling) are put in hand early.

With the Pituitary Body.—All observers are agreed that a striking effect is caused by removal or atrophy of the thyroid upon the pituitary body: which not only undergoes general enlargement, but also exhibits well-marked indications of increased secretion. These changes will be described when the pituitary is dealt with.

What part, if any, concomitant removal of parathyroids may take in promoting the changes in the pituitary is not certainly known. According to Halpenny and Thompson,⁷ some of the alterations which have been described in the pituitary occur if the parathyroids alone are extirpated. But other observers have failed to find any changes in the pituitary after parathyroidectomy. J. A. Larson⁸ states that administration of the anterior lobe of the pituitary has a beneficial effect on thyroidectomised rats, causing their life to be prolonged indefinitely. It must, however, be borne in mind that rats withstand loss of the thyroid better than most animals.

With the Thymus Gland.—Reference has already been made to the anatomical and developmental relationship between thymus and thyroid, to the effect of thyroid feeding of a pregnant animal upon the growth of the thymus of the foetus, and to the supposed effect of the thymus in assisting to produce the symptoms of exophthalmic goitre: indeed its removal by operation has been recommended and even practised in that affection (see p. 50). In view of these circumstances some authorities believe that there exists a mutual relationship between the two organs, and that they exercise—by internal

¹ He states this to be the case also with a preparation of thyroid (Hofmann and La Roche) termed "thyreoglandol," which according to the manufacturers contains neither protein nor iodine.

² *Wien. klin. Wochenschr.*, 1908, and *Zeitschr. f. klin. Med.*, lxvi., 1908.

³ *Journ. Exper. Med.*, xi., 1909.

⁴ *Amer. Journ. Physiol.*, xxv., 1909; Underhill, *ibid.*, xxvii., 1911.

⁵ *Kyoto Igaku Zasshi*, 1917. (See *Endocrinology*, ii., 1918, 325.)

⁶ *Brit. Journ. Exper. Path.*, i., 1920, and 6th *Sci. Report of Imperial Cancer Research Fund*, 1919.

⁷ *Anat. Anz.*, xxxiv., 1909.

⁸ *Amer. Journ. Physiol.*, xlix., 1919, and liii., 1920.

secretions—an excitatory influence upon one another. In conformity with this it has been stated that increase or diminution in size of the two organs frequently go hand in hand. But this can only be early in life, for under ordinary conditions of growth and development the thymus is undergoing retrogression whilst the thyroid is becoming more active in its functions. Moreover, the normal variations in both organs are so considerable, and at present, in spite of many observations, so little is accurately known regarding the conditions under which they occur, that it will be wise to reserve judgment as to their mutual relations. E. R. Hoskins¹ finds that the thymus enlarges with thyroid feeding, the change affecting only the cortex. We have seen that it is also usually enlarged in exophthalmic goitre. Thyroidectomy, on the other hand, is said to promote involution of the thymus.²

¹ *Journ. Exper. Zool.*, xxi., 1916.

² R. Pigache and G. Worms, *Arch. d'anat. microsc.*, xii., 1910.

CHAPTER VIII

THE PARATHYROIDS

THESE are quite minute organs, four in number, each averaging 6–7 mm. long, 3–4 mm. broad, and 1·5 to 2 mm. thick, and weighing about 0·03 gram (half a grain). In rare cases more than four are found of about the dimensions above given, although smaller accessory parathyroids are not uncommon (see p. 16).

The parathyroids are developed as solid outgrowths of the epithelium of the 3rd and 4th visceral pouches on each side (fig. 2), that from the 3rd pouch giving rise to the lower, and that from the 4th to the upper, parathyroid. From the same pouches the thymus is also derived. The parathyroids were first recognised as organs distinct from the thyroid by Sandström;¹ their physiological importance was determined by E. Gley.² Gley was at first inclined

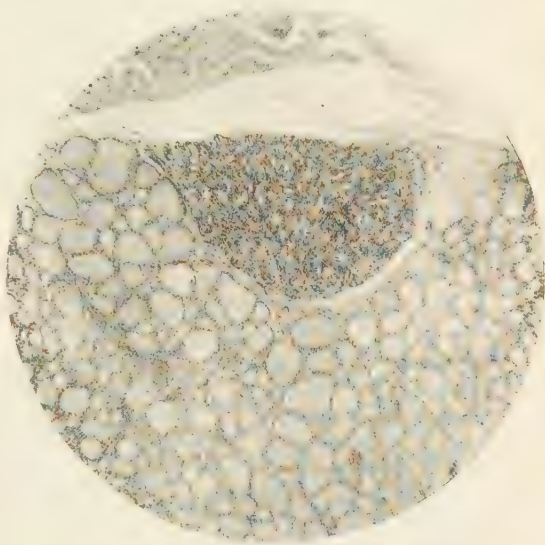


FIG. 35.—Section of parathyroid and adjacent thyroid tissue (rat). Magnified 50 diameters. The vesicles of the thyroid are filled with colloid. The parathyroid is of the trabecular type.

to believe that the parathyroids represent embryonic thyroid substance, but was subsequently led to the conclusion that they are entirely independent organs. They are usually either attached to (figs. 35 to 37) or altogether embedded in (fig. 38) the substance of the thyroid (p. 14).

Structure of Parathyroids.—The parathyroids are composed of epithelium-like cells (figs. 39 to 41), which either form a compact mass (fig. 39) or are divided up into lobules or trabeculæ (fig. 40) by strands of vascular connective tissue. These differences of structural appearance may sometimes be observed even in different parts of the same gland. The interstitial connective tissue conveys the vessels, which mainly take the form of sinus-like capillaries.

¹ *Läkareför. Förhandl.*, Upsala, 1880.

² *C. r. soc. biol.*, 1891–1897.

There is a capsule of areolar tissue sending in processes to join the interstitial tissue of the organ: plain muscle cells have been described in this; it may

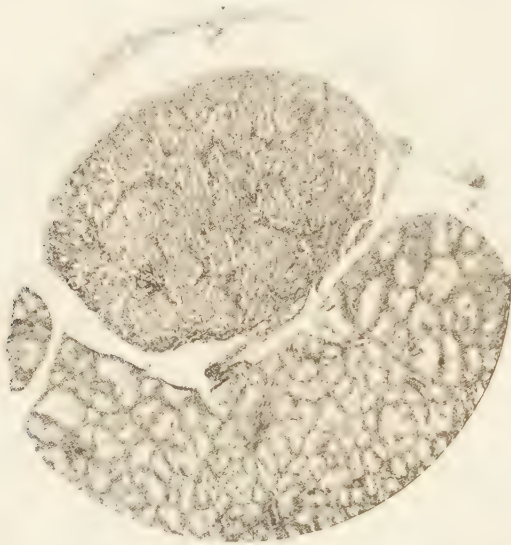


FIG. 36.—The same, from another preparation. The thyroid vesicles are not distended with colloid; their cells are columnar.

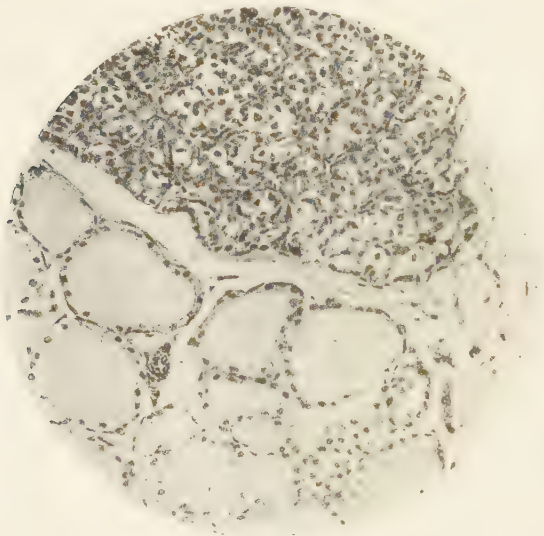


FIG. 37.—Part of a section of thyroid and parathyroid (rat). Magnified 200 diameters. In this gland the vesicles of the thyroid are distended with colloid. The parathyroid is of the trabecular type.

also contain fat-cells. Besides the ordinary or principal cells of the gland—which are small and either clear or somewhat granular—others occur which

are considerably larger and contain oxyphil granules, staining with eosin

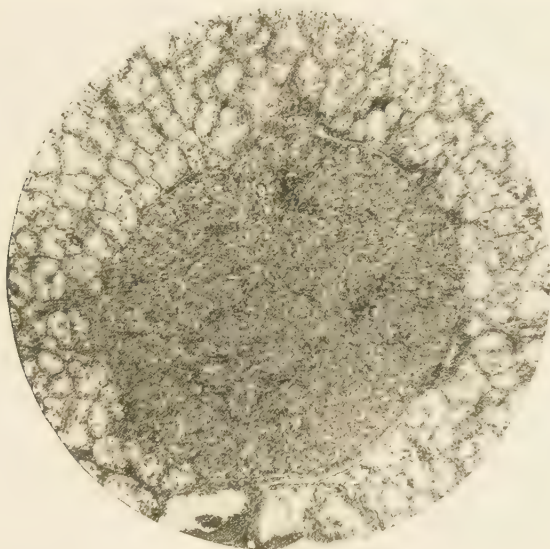


FIG. 38.—Section of an internal parathyroid (rat). Magnified 50 diameters. (An internal parathyroid is not often found in the rat, although common in many animals.) The vesicles of the thyroid are not distended with colloid in this preparation.

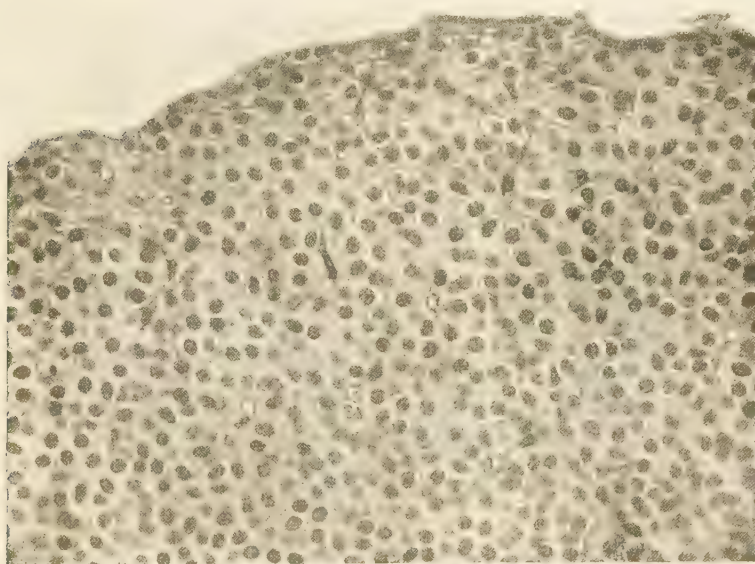


FIG. 39.—Section of parathyroid (cat). Magnified 400 diameters. This is a good illustration of the compact type of gland.

(Welsh): these only appear after the tenth year in man. Probably they represent a functional stage of the ordinary cells, since transitional forms occur.

Both kinds of cell contain fatty granules, which increase in number with age.

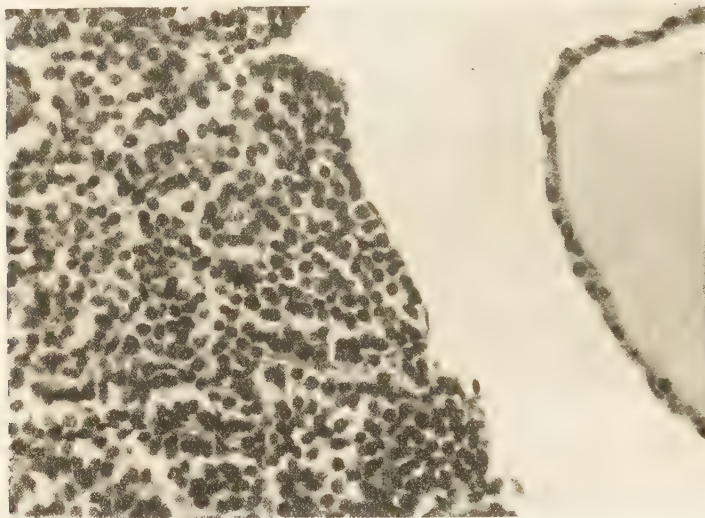


FIG. 40.—Section of parathyroid of dog. Magnified 400 diameters. This shows a looser arrangement of the trabeculae than the gland represented in fig. 39. On the right is part of one of the vesicles of the thyroid.

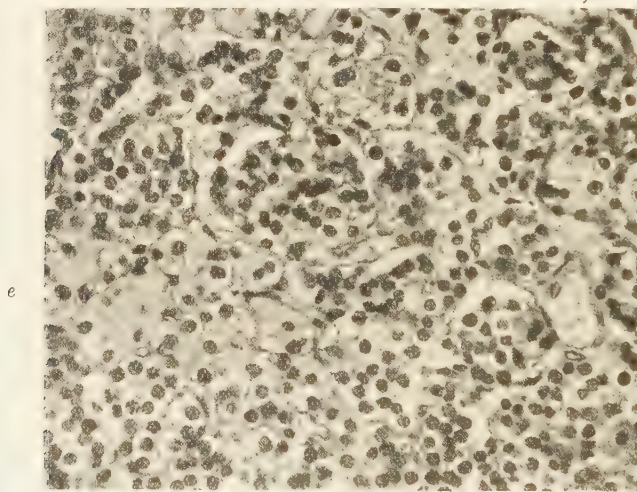


FIG. 41.—Section of parathyroid of man. Magnified 400 diameters. On the left is a strand of eosinophil cells (*e*). (Figs. 39, 40, and 41 are from specimens prepared by M. Kojima.)

A considerable amount of glycogen has also been detected in them, especially in the principal cells.¹

¹ H. Petersen, *Arch. f. path. Anat.*, clxxiv., 1903.

Vesicles containing colloid material similar in appearance to those of the thyroid, but usually smaller, are occasionally found in the parathyroids. They increase in number with age; sometimes the colloid is found between the cells, not enclosed within a vesicle. Whether it is of the same chemical nature as that of the thyroid is not established, but it is probably different, as it appears to contain no iodine, although some observers state that they have detected traces. After complete removal of the thyroid, in the parathyroids which had been left colloid-containing vesicles were found by Vincent and Jolly in larger number than usual (fig. 42).¹ Biedl has made a similar observation, viz. that the parathyroids which remain are enlarged, and have numerous colloid-containing vesicles.²

The parathyroids usually remain unaltered in myxœdema, in which affection the thyroids are atrophic. Forsyth³ has, however, described one case which was an exception to this rule. Biedl has also recorded the development of colloid-containing vesicles in the parathyroid in a case of atrophy of the thyroid in man. An enlargement of the parathyroids following thyroidectomy has been described by Kamo,⁴ who, however, found no change in structure.

The parathyroids are amongst the most vascular organs in the body. They are supplied each by a special arteriole from the inferior thyroid artery or from its anastomic branch (see fig. 4).⁵ The sinus-like capillaries come into close relationship with the epithelial cells of the gland.

The nerves of the parathyroids, which probably like those of the thyroid take origin from the sympathetic, have been traced both to the vessels and to the cells of the gland, but it is not known how they influence the secretion.

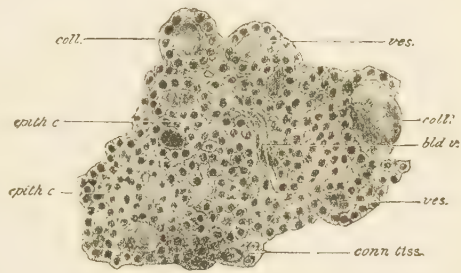


FIG. 42.—Section of parathyroid of cat after previous removal of thyroid. (Vincent and Jolly.) Vesicles which contain colloid are developed within the gland. These may, however, be found in the parathyroids under normal circumstances.

¹ *Journ. Physiol.*, xxxii., 1904, and xxxiv., 1906.

² *Innere Sekretion*, 1916.

³ *Trans. Clin. Soc.*, xl., 1907.

⁴ *Kyoto Igaku Zasshi*, 1917.

⁵ See Halsted and Evans, "The Parathyroid Glandules and their Blood-Supply," *Ann. Surg.*, xlv., 1907.

CHAPTER IX
THE PARATHYROIDS (*continued*)

EFFECTS OF REMOVAL: PARATHYROIDECTOMY. TETANY

*Parathyroidectomy.*¹—If the removal is complete, *i.e.* if it includes all four parathyroids, most animals soon die; some within a few days, others within a few weeks. If one of the four parathyroids is left, or if there should be an accessory parathyroid which has not been included in the operation, the operated animal may live for a considerable time, but is liable to develop the symptoms characteristic of tetany on small provocation (latent tetany). These symptoms

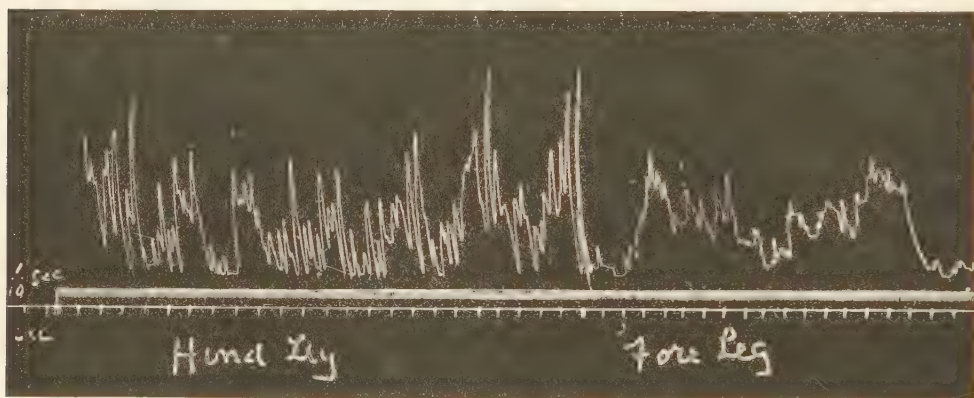


FIG. 43.—Record of tremors in hind- and fore-leg of dog in tetania parathyreopriva. Time in 0.1 sec. and in 1.0 sec. (Noël Paton, Findlay, and Watson.)
The spinal cord has been divided in this animal.

vary greatly in different animals. They are usually more pronounced in the dog than in the cat, and more in carnivorous than in herbivorous animals. In the dog for the first day or two there is nothing noticeable except loss of appetite. The most marked and constant early change is an alteration in disposition, the animal becoming depressed and sluggish.² There may then supervene a stiffness of the muscles of the hind limbs of the nature of an extensor spasm (spasticity); the head is often dorsiflexed; in monkeys there is flexion of the fingers and at the wrists. The stiffness of the muscles

¹ The history of parathyroidectomy is given by Sutherland Simpson in *Endocrinology and Metabolism*, edited by L. F. Barker, 1922.

² The condition persists between the fits until death (Noël Paton and Findlay, *Quart. Journ. Exper. Physiol.*, x., 1917, p. 220). For further details this paper should be consulted.

is associated with fibrillar contractions or tremors, and chorea-like jerking movements (fig. 43), and later with cramp-like and clonic contractions, with eventually convulsive fits; these may be of considerable violence, and alternate with intervals of quietness, not to say depression.¹ In progression the limbs and tail are stiff, and exhibit quiverings and eventually clonic contractions. Cats sometimes show a peculiar "paw-shaking" during progression. In monkeys, if, as is not infrequent, the animal dies in a fit, the hands are found in a characteristic position with the fingers flexed and the thumb adducted



FIG. 44.—Characteristic position of hand of monkey in a fit of tetania parathyreopriva. (Noël Paton and Findlay.)

(fig. 44). The irritability of the peripheral nerves and of the skeletal muscles to galvanic stimuli (*spasmophilia*) is markedly increased (to four times or more): this is regarded as almost pathognomonic of tetany, whether operative or idiopathic, but is not proportionate to the severity of the symptoms, which are mainly due to functional changes in the central nervous system. The increased excitability is not confined to the ordinary nerves, but affects the autonomic system as well, for the excitability of the sympathetic is also increased.² The reflexes are sometimes increased, sometimes decreased, sometimes unaltered. There are often disturbances of balance, occasionally with forced (cerebellar) movements. A diminution of sugar in the blood and of glycogen in the liver has been noted,³ and there may be acidosis with retention

¹ These alternations are characteristic (Simpson).

² R. G. Hoskins and Wheelon, *Amer. Journ. Physiol.*, xxxiv., 1914. A. J. Carlson found the neuro-muscular mechanisms of the digestive tract to be unaffected (*ibid.*, xxx., 1912).

³ Underhill and Blatherwick, *Journ. Biol. Chem.*, xviii., 1914.

of phosphorus. The hair tends to be shed. In the rat Erdheim¹ found that the growing incisors fail to be properly calcified.² During a fit the pulse is quickened and the heart-beat exaggerated. There is profuse salivation; sometimes vomiting and diarrhoea. The body temperature may rise two or three degrees centigrade. The paroxysms are usually accompanied by rapid, gasping respirations which may even be synchronous with the heart-beats: this has been attributed to the hypersensitiveness of the phrenic, causing it to be stimulated by the action-currents of the heart.

Death may occur within a few days, and is usually associated with cramp of the respiratory muscles. But the affection may last a long time. In chronic cases the animal becomes emaciated from loss of appetite and partial refusal of food. The fits are sometimes frequent, but more often recur at long intervals; the animals usually eventually succumb during a convulsion. Spontaneous recovery may occur. This is generally ascribed to the hypertrophy of an accessory gland. After death from tetany, hæmorrhages have frequently been found in the parathyroids.³ But they are not confined to these organs,⁴ and there is usually nothing abnormal to be detected in them.

The syndrome is usually spoken of as *operative tetany* or *tetania parathyreopriva*; this is in no way synonymous with tetanus. It was often observed in man as the result of the removal of thyroid tumours in the days before the physiological significance of the parathyroids was recognised.⁵ The symptoms usually appeared between the third and sixth days, and their severity depended upon the number of parathyroids removed. They were more liable to occur after operation for exophthalmic than for endemic goitre.

The most acute symptoms are exhibited by carnivora, such as dogs, cats, foxes, and wolves.⁶ Some species of animal (*e.g.* sheep) exhibit no symptoms whatever when the operation is performed on the adult. Horsley stated that this is the case with birds and rabbits; but according to Gley, the latter are affected if care is taken to find and remove all parathyroids. Typical tetany is seen in hens which have been parathyroidectomised.⁷

Vincent and Jolly found that rats and guinea-pigs do not seem to suffer from removal of their parathyroids, but H. Cristiani⁸ and J. Erdheim⁹ both obtained tetania parathyreopriva in rats, although in them it takes much longer to produce a fatal result than in most animals.

According to de Mira,¹⁰ guinea-pigs deprived of the whole thyroparathyroid apparatus also invariably die, but the period after operation may vary from

¹ *Zeitschr. f. Path.*, 1911.

² Deficient calcification of the teeth has also been noticed in children affected by idiopathic tetany (see p. 80).

³ W. Halberfeld, *Virch. Arch.*, cciii., 1911.

⁴ Carlson and Jacobson, *Amer. Journ. Physiol.*, xxviii., 1911; W. B. Kosh, *Journ. Exper. and Clin. Med.*, i., 1917.

⁵ v. Eiselsberg, *Ueber Tetanie im Anschluss an Kropfoperationen*, Wien, 1890.

⁶ Vincent and Jolly, *Journ. Physiol.*, xxxii., 1904, and xxxiv., 1906.

⁷ Doyon and Jouty, *C. r. soc. biol.*, 1904.

⁸ *Arch. de physiol.*, 1893, and *C. r. soc. biol.*, xlix., 1897 (with Ferrari).

⁹ *Wien. klin. Wochenschr.*, 1906.

¹⁰ *Journ. de physiol.*, xviii., 1920.

forty-eight hours to nearly three months. When death results soon, tetany is manifested: otherwise the chief symptom is apathy. It may be that when the survival is prolonged one or more concealed parathyroids have been overlooked. Pfeiffer and Mayer¹ obtained tetany in mice. According to Vincent and Jolly, badgers are totally unaffected by complete removal of both thyroids and parathyroids. Vassale and Generali² found that when the thyroids were removed along with the parathyroids the symptoms caused by removal of the parathyroids were less acute than when the parathyroids alone were extirpated.

It is possible that insufficient attention has been paid to age by many who have experimented on the subject. For it is certain that young animals are much more susceptible to parathyroidectomy than adults.³ This is strikingly exemplified in experiments by Sutherland Simpson⁴ on sheep and lambs. He found that sheep usually show no symptoms as the result of complete removal of thyroids and parathyroids, while lambs exhibit both symptoms of tetany and arrest of development with supervention of cretinism. Adult goats, on the other hand, may exhibit well-marked tetania parathyreopriva.⁵ In monkeys this condition has sometimes been missed, but it occurs if the removal of the parathyroids is complete.

It must not be forgotten that it is not easy to find or remove all the parathyroids. Especially is this the case where one or more are liable to be concealed within the thymus. This will account for some of the discrepancies in the experimental results, but not for those obtained in operations on young and old animals of the same species: it is, however, to be noted that the parathyroids are more distinct and more easily found in young animals.

Tetania parathyreopriva is sooner evident in wild than in white rats, and sooner in excitable white rats than in tame or non-excitable animals. The condition of the nervous system therefore counts for something in its production. Hammett has found that the growth of rats is retarded by removal of the parathyroids, although to a less extent than by removal of the thyroid, the effect of both being more marked in females than in males. The result of parathyroid removal on growth is also less continuous than that of thyroid removal, and is an indication rather of the effect of toxic products which are not eliminated than of the removal of a material which stimulates growth and cell-activity.⁶

The dependence of tetany upon the integrity of the parathyroids was conclusively demonstrated by Biedl,⁷ who transplanted the parathyroids of a dog into the spleen of the same animal and subsequently removed the thyroids. No symptoms of tetany showed themselves during some months after the operation, although the usual symptoms resulting from removal of thyroid became manifest. On now removing the spleen with its implanted para-

¹ *Mitteil. a. d. Grenzgeb. d. Med. u. Chir.*, xviii., 1907.

² *Arch. ital. de biol.*, xxv. and xxvi., 1896, and xxxiii., 1900; *Rif. med.*, 1897.

³ V. Horsley, *Proc. Roy. Soc.*, xl., 1886. Morel (*Les parathyroides*, Paris, 1912) found that kittens do not develop tetany if parathyroidectomised while suckling, but as soon as they are weaned the symptoms appear.

⁴ *Quart. Journ. Exper. Physiol.*, vi., 1913. See also his article in *Endocrinology and Metabolism*, 1922, vol. i., p. 522.

⁵ Christens, *C. r. soc. biol.*, lviii., 1905.

⁶ *Amer. Journ. Physiol.*, lxiii., 1923.

⁷ *Innere Sekretion*, iii. Aufl., Teil i., 1916, p. 136.

thyroids, severe, and eventually fatal, tetany supervened within twenty-four hours. Examination of the removed spleen showed that some at least of the transplanted parathyroids had "taken" and exhibited their normal structure. In some of these experiments tetany resulted without removal of the spleen. In these post-mortem examination showed that the parathyroid grafts had not taken, but had undergone degeneration. A positive result, *i.e.* supervision of tetany, was sometimes obtained with homoio- in place of auto-transplantation. the parathyroids of other dogs being used for transplantation. But in all cases of transplantation such grafts "take," as is well known, with much greater difficulty than grafts from the same individual. Similar results were obtained by Halsted¹ from auto-transplantation, but only after entire removal of all parathyroids from their natural situation. Halsted implanted the removed parathyroids not only into the spleen but also into the thyroid gland and abdominal muscles.

MacCallum and Voegtlin² state that the effects of parathyroidectomy can be removed by injection of extract of parathyroid. The extract has also been used with some success in man by Halsted and others.³ The same result was obtained by MacCallum and Voegtlin from the administration of calcium salts, both subcutaneously and by the mouth; they regard tetany as caused by a diminished calcium content of the blood. Biedl, however, states that calcium salts do not prolong life after the operation. According to Carlson and Jacobson, the action of calcium salts, when it occurs, is merely like that of other substances which decrease the excitability of the nervous system.⁴ It is stated that tetany in dogs can be absolutely controlled by the oral administration of 1.5 g. calcium lactate per kilo daily.⁵

W. F. Koch states that in dogs dying as the result of parathyroidectomy there are extensive ante-mortem clots in the heart and in the vena cava inferior; fatty degeneration of liver cells; congestion of kidney; oedema and congestion of lungs; and chromatolysis in the cells of the motor area of the brain; besides changes in the cell-nuclei. He also obtained evidence of destruction and new formation of erythrocytes.⁶

THE PARATHYROIDS IN DISEASE

*Idiopathic Tetany.*⁷—A condition of tetany is associated in man with atrophy or pathological degeneration of the parathyroids.⁸ It occurs most frequently in childhood, and is probably caused by congenital atrophy

¹ *Journ. Exper. Med.*, xi., 1909.

² *Ibid.*, and *Johns Hopkins Hosp. Bull.*, xlx., 1908.

³ W. S. Halsted, *Amer. Journ. Med. Sci.*, cxxxiv., 1907; W. R. Grove and H. W. C. Vines, *Brit. Med. Journ.*, 1921 and 1922; see also Vines, *Journ. Physiol.*, lv., 1921.

⁴ *Amer. Journ. Physiol.*, xxviii., 1911.

⁵ Luckhardt and Goldberg, *J. Amer. Med. Assoc.*, xx., 1920.

⁶ *Journ. Biol. Chem.*, xv., 1913. Mollgaard (*Skand. Arch. f. Physiol.*, xxviii., 1912) describes chromatolysis of the cells of the ventral horn of the cord as a result of parathyroidectomy.

⁷ For the clinical aspects of tetany, see L. F. Barker, in *Endocrinology and Metabolism*, vol. i., 1922. The term "tetany" seems first to have been used by Corvisat in 1852.

⁸ M'Carrison believes that the changes in the parathyroids are usually brought about by intestinal toxins (*The Thyroid Gland*, 1917, p. 152).

of the glands. Sometimes the condition comes on in older children, and occasionally in adults, often as the result of some general affection such as tubercle. In all cases one of the first signs is the increase of excitability of the peripheral nerves to galvanic stimulation; as well as to mechanical stimuli, as indicated by Chvostek's and Trousseau's phenomena.

In Chvostek's test¹ the seventh nerve is percussed just in front of the external auditory meatus, producing contraction of the facial muscles. In Trousseau's test² the arm is compressed circularly above the elbow. This produces a peculiar position of the fingers and thumb, which are flexed at the metacarpophalangeal joints, the thumb being partly covered by the fingers. The condition is brought about by a spastic contraction of the muscles, and was termed by Trousseau "main d'accoucheur" (fig. 45).



FIG. 45.—Outline sketch showing the position of the thumb and fingers in a fit of idiopathic tetany in man. (After Lewandowsky.)

The galvanic hyperexcitability of the peripheral nerves in idiopathic tetany was first described by Erb (1874), and has since been the subject of numerous investigations, of which those of Harvier³ may be specially mentioned. The subject is one of diagnostic importance and of much interest, but for the numerous details which have accumulated regarding it the reader must be referred to works on clinical medicine.⁴

A frequent feature of infantile tetany is spasm of the glottis, impeding the entrance of air into the lungs; and with this there is often spasm of the bronchial musculature. At all ages there are muscular tremors and the liability to fits which also characterise tetania parathyreopriva, but in tetany of children the contractions tend to be tonic rather than clonic, taking the form of carpopedal spasms, with the characteristic position of the hands and fingers shown in fig. 45, or like that seen in the parathyroidectomised monkey (fig. 44). Besides this spastic condition of the arm muscles there also occurs a flexion of the toes.

In certain localities, *e.g.* Vienna, Heidelberg, an endemic form of tetany has

¹ *Deutsch. Med. Woch.*, xxxv., 1909.

² *Gaz. des Hôpitaux*, Nov. 6, 1851.

³ *Recherches sur la tétanie*, etc., Paris, 1909.

⁴ A résumé of the chief facts will be found in the second French edition of this work, translated by Drs Laroche and Richard, Paris, 1921, p. 27. A comparison of idiopathic with operative tetany will be found in the article by Noël Paton and Findlay in the *Quart. Journ. Exper. Physiol.*, x., 1917. These authors state that the hyperexcitability to mechanical stimulation seen in idiopathic tetany is absent in operative tetany.

been described, becoming epidemic at certain seasons of the year. It is said to affect especially workmen belonging to certain trades. Its presence may only be indicated by increased excitability of the peripheral nerves, but all the symptoms of tetany—even severe fits—may show themselves. In India endemic tetany has been found chiefly in goitre localities, and it is suggested that goitrous tumours of the thyroid may by pressure lead to partial atrophy of the parathyroids.¹

Tetany, whether operative or idiopathic, is without doubt due to deprivation or disease of the parathyroids, for it will occur when these alone are involved. It varies greatly in severity, may be acute or chronic, and often takes on an intermittent character, showing itself only when from some accidental circumstance the general irritability of the nervous system is increased (latent tetany, see p. 72). These variations are probably related to the number of parathyroids removed or affected by disease, or by the extent of their atrophy. It is the lower neurones which are principally affected. The change first shows itself at the nerve-endings of the motor nerves, which become hyperexcitable. This is also the case with the muscle fibres themselves; the endings of the sensory nerves are also involved. The nervous symptoms are not arrested by ablation of the cerebral cortex.² This indeed increases the violence of the symptoms from loss of inhibitory influences. Biedl states that the nervous symptoms are increased on the side opposite to the ablation when this is unilateral; with cerebellar lesion he finds an increase on the same side. Noël Paton and Findlay came to the conclusion that integrity of the cerebellar arc is necessary for the manifestation of tonic extensor spasm but not of tremors and jerkings.³ If a section is made across the middle of the cord both fore- and hind-limbs show the characteristic jerking movements, but their rhythm may be quite different (fig. 43). After the transection the tonic contractions of the muscles cease below the section, but the muscular tremors and twitchings proceed as before above it. Section of dorsal roots does not affect the tremors.⁴ Section of the motor nerves abolishes them. If the blood of a parathyroidectomised dog is allowed to circulate in the vessels of a normal dog, muscular tremors are produced in the latter.

Idiopathic tetany is sometimes relieved by injection of parathyroid extract, and also by administration of thyroid substance: it is uncertain if this last result is due to included parathyroid, probably not. But when tetany has been produced by *total extirpation* of all parathyroid tissue it can apparently only be cured by a successful graft of a parathyroid from an animal of the same species. Occurring after complete removal of the thyroparathyroid apparatus in man, tetany may be sufficiently serious to

¹ M'Carrison, *The Thyroid Gland*, 1917.

² V. Horsley, *Virchow's Festschrift*, 1891; see also O. Lanz, *Volkman's Sammlung*, 1894. Lanz points out that the disturbances of balance which often occur indicate abnormal cerebellar action.

³ Noël Paton, Findlay, and Watson, *op. cit.*

⁴ H. J. Mustard, *Amer. Journ. Physiol.*, xxix., 1912.

threaten life, unless measures are taken to combat the effects of parathyroid loss.¹

In order to prevent the accession of tetany in operations for removal of thyroid tumours it is usually considered necessary to leave at least two of the four parathyroids. In one dog experimented on by Edmunds, he found that a single parathyroid was sufficient to prevent the onset of tetany (the three others and both lobes of the thyroid having been removed): on extirpation of the remaining parathyroid the animal speedily developed tetany.

Animals with insufficient amount of parathyroid tissue may not suffer from tetany under ordinary circumstances, but the symptoms may come on under special conditions, such as the supervention of pregnancy.² Thus Vassale observed, in a bitch from which three of the four parathyroids had been removed, that the animal was especially subject to fits of tetany during pregnancy³ and lactation.

The character of the food also influences the onset of the symptoms, flesh foods being much more apt to bring on tetany than vegetable or milk diets.

An interesting fact has been recently noted, viz. that prolonged voluntary hyperpnoea (forced breathing) brings on many of the symptoms which are characteristic of tetany—carpopedal spasms, increase of muscle tonus passing into spasticity, hyperexcitability of peripheral nerves, Trousseau's phenomenon, Chvostek's sign, and in one instance a complete tetany-convulsion.⁴ Profuse sweating, tingling sensations, dizziness, and frontal headache have also been observed.

¹ See Morel, "La greffe parathyroïdienne," *Arch. gen. de Chir.*, vi., 1912. A case in which all possible remedies, and grafts from various animals, including a monkey, were tried without avail, but which was rapidly and completely cured by the implantation into the subcutaneous tissue of parathyroids obtained from a subject very soon after death from an accident, is described by W. H. Brown in the *Annals of Surgery*, vol. liii., 1911. Several similar cases have been reported.

A. F. Herz (*Endocrinology*, ii., 1918) describes a case in which parathyroid feeding appeared successful in combating the nervous and other symptoms produced by surgical removal of the thyroid and parathyroids. Other instances are mentioned by Simpson in Barker's *Endocrinology and Metabolism*, 1922.

² G. Vassale, *Arch. ital. de biol.*, xxx., 1897. Confirmed by Marsaglia (*Endocrinology*, v., 1921), who suggests that parathyroid insufficiency may be one of the determining causes of the eclampsia of pregnancy.

³ This is contrary to what might be expected, considering that the mother would have had the parathyroids of the fetuses to draw on. Moreover, in cats Carlson and Jacobson obtained contrary results (*Amer. Journ. Physiol.*, xxviii., 1911). In any case, we do not know if the parathyroids are functional before birth; or, supposing them to be functional, if the material they yield can pass through the placental villi into the maternal blood. Animals which have suffered complete parathyroidectomy do not, as a rule, become pregnant, but ewes were found by Sutherland Simpson to become pregnant and sometimes even to bring forth healthy lambs—although in most cases the lambs died *in utero* and most of the mothers also succumbed (article, "The Parathyroid Glands," in Barker's *Endocrinology and Metabolism*, 1922).

⁴ J. B. Collip and P. L. Backhus, *Amer. Journ. Physiol.*, li., 1920; Grant and Goldman, *ibid.*, lii., 1920. Sporadic observations of a similar nature had been previously recorded, e.g., by H. M. Vernon in *Proc. Physiol. Soc. in Journ. Physiol.*, xxxviii., 1909; Yandell Henderson, *Amer. Journ. Physiol.*, xxvi., 1909; and L. Hill and M. Flack, *Journ. Physiol.*, xl., 1910. Possibly the effects of forced respiration are due to the alteration it produces in the pH of the blood. S. B. Grant (*Amer. Journ. Physiol.*, lxvi., 1923) finds they are not due to anoxæmia.

Tetany has occasionally been seen in the later stages of pregnancy in women and during lactation, and has apparently then been caused by a pathological change of the parathyroids.¹ It is also found to result from acute infectious disorders, from general nutritional disturbances, and to occur in the course of thyroid disease and certain affections of the central nervous system.

Besides those of idiopathic tetany various other clinical symptoms have been associated with pathological changes in the parathyroids, and referred (1) to atrophy or diminished secretion (*hypo-parathyroidism*), (2) to enlargement or increased activity (*hyper-parathyroidism*), (3) to altered secretion (*dys-parathyroidism*). The first condition gives rise to manifestations resembling those of tetania parathyreopriva. In some such cases degenerative changes or hæmorrhages have been observed in the parathyroids. Other cases have been recorded in which changes of a similar character have been found post-mortem in the parathyroids without symptoms of tetany having been noticed during life, but it is unlikely that all four organs were affected or destroyed. Various attempts have been made to associate conditions showing increase of response to reflex or to cortical stimuli, *e.g.* such as occur in Thomsen's disease (*myotonia congenita*), in Parkinson's disease (*paralysis agitans*), and in *chorea* with a condition of chronic deficiency of parathyroid secretion. It is stated by Berkeley² that cases of *paralysis agitans* are benefited by administration of parathyroid, and the gland has also been recommended in *chorea*, epilepsy, and eclampsia. It has also been suggested that pseudo-paralytic conditions, such as *myotonia periodica* and *myasthenia gravis*, are due to chronic increase of the secretion. But the evidence in support of the view that these affections are related to abnormalities of the parathyroids is not convincing. Cases of osteomalacia have been found to be associated with hyperplasia (adenoma) of parathyroids.

Tumours of the parathyroids are rare, and are only recognisable after operation, since they simulate goitrous swellings of the thyroid. They are characterised by containing an unusual amount of glycogen, which is a constant constituent of the chief cells of the parathyroids. Tumours of parathyroid tissue have sometimes been found in the anterior mediastinum.

Effects on Metabolism.—Chronic parathyroid tetany is always accompanied by rapid diminution in weight and general emaciation, indicating that the nutrition of the body as a whole is seriously affected.³ The emaciation is due, at least in part, to incidental circumstances, such as loss of appetite and the supervention of diarrhœa. These conditions may appear, even in the absence of actual tetany, as a result of insufficiency of parathyroid secretion such as occurs when the arteries of the glands are ligatured.⁴ An observation which has frequently been made after parathyroidectomy is the occurrence of changes in the hair and nails, and also in the growth and structure of the bones and teeth. These changes are only seen if the animals survive the operation for some time. They occur in idiopathic tetany. The calcification of both dentine and enamel of the teeth is delayed and imperfect, and they are

¹ W. Halberfeld, *Virch. Arch.*, cciii., 1911.

² *Med. Rec.*, xc., 1916.

³ M. Parhon finds that after parathyroidectomy the liver and muscles of dogs contain less glycogen than in normal controls (*C. r. soc. biol.*, lxxxiii., 1920).

⁴ Thompson, Leighton, and Swarts, *Journ. Exper. Med.*, xi., 1909.

unusually brittle. In the skeleton the bones remain smaller than in the controls; also the healing of fractures is delayed.¹ If these changes are the direct result of absence or atrophy of the parathyroids, there is reason for believing that the parathyroids influence calcium metabolism in some way which is not understood.

The changes in calcium metabolism are different from those met with in rickets, but true rachitic changes often accompany infantile tetany; or, in other words, amongst children with rickets a large proportion show symptoms of tetany.² It has been suggested that the cause may be a common one, viz. lack of vitamins in the food,³ which may, it is supposed, affect the parathyroids. As further indication of a connexion between rickets and parathyroids, it is found that rats affected by rickets have their parathyroids greatly enlarged, with many mitoses amongst their cells.⁴

The endemic (and occasionally epidemic) form of tetany which affects the workers in certain localities (see p. 77) has been ascribed to chronic ergot poisoning, since it is chiefly seen in districts where rye bread is consumed (Fuchs). It may, however, be due to lack of vitamins.⁵

It is stated that inorganic phosphorus is found in larger amount than usual in the blood after parathyroidectomy.⁶

Bieling found that in rachitic infants subcutaneous injection of parathyroid extract caused not only retention of phosphorus but also of calcium and magnesium.⁷

W. G. MacCallum ascribed the nervous symptoms in tetany to a deficiency of calcium in the system, since it is known that salts which precipitate calcium increase the excitability of nervous and muscular tissue, whilst salts of calcium diminish it. The evidence as to the condition of calcium in tetany is, however, conflicting. Some observers⁸ have described an actual increase of calcium in idiopathic tetany and in parathyroidectomised animals, both in the blood and urine; whereas others have found calcium deficiency in the blood,⁹ and this is known to be a cause of muscular tremors.

H. Bergstrand¹⁰ found no difference in the calcium content of the blood in children with tetany as compared with normal children; but Trendelenburg and

¹ L. Fleischmann, *Wien. klin. Wochenschr.*, xxi., 1908; J. Erdheim, *Zeitschr. f. Path.*, vii., 1911; Tokofuku, *ibid.*, 1911; J. Hohlbaum, *Ziegler's Ber.*, liii., 1912; A. Canal, *Arch. p. l. sci. med.*, 1910; L. E. Morel, *C. r. soc. biol.*, 1909, 1910, 1911. M. Kojima found calcium in the urine increased in rats after parathyroidectomy (*Quart. Journ. Exper. Physiol.*, xi., 1917).

² Ferguson, quoted by Noël Paton and Findlay, *op. cit.*

³ E. Mellanby, *Lancet*, 15th March 1919; *Brit. Med. Journ.*, 4th Nov., 1922.

⁴ Erdheim, *Wiener Denkschr.*, xc., 1914.

⁵ C. Funk and M. Douglas, *Journ. Physiol.*, xlvii., 1914.

⁶ I. Greenwald, *Amer. Journ. Physiol.*, xxviii., 1911; *Journ. Biol. Chem.*, xiv., 1913, and xxv., 1917; *Biochem. Zeitschr.*, l. and liv., 1913.

⁷ *Biochem. Zeitschr.*, lxiii., 1914.

⁸ W. Stöltzner, *Jahrb. f. Kinderheilk.*, lxiii., 1906; *Neurol. Centrbl.*, xxvii., 1908; *Monatschr. f. Psych.*, xxv., 1909.

⁹ F. P. Underhill, *Journ. Med. Res.*, i., 1922. H. A. Salvesen (*Proc. Soc. Exper. Biol.*, xxii., 1923) considers this drop in blood-calcium the essential chemical feature of parathyroid insufficiency.

¹⁰ *Nederl. Tijd. v. Geneesk.*, 1919.

Goebel,¹ using the frog heart as an indication of Ca-concentration in serum, state that there is a deficiency of Ca in tetania parathyreopriva, which can be compensated by addition of Ca to the perfused fluid. MacCallum and Voegtlin² got considerably less calcium in the blood of parathyroidectomised dogs than in that of normal animals. MacCallum and Vogel³ found, on perfusing a limb of a normal dog with blood from a "tetany" dog, the excitability of the muscle-nerve preparation increased above normal. This is probably due to the presence of an excitatory substance (guanidine) in the "tetany" blood, but MacCallum and Vogel supposed it to be due to diminution of calcium. Trendelenburg⁴ determined that the amplitude of the contractions of the isolated frog heart was diminished by serum of "tetany" cats as compared with that of normal cats, and concluded that this is due to a diminution of Ca-ions. Berkeley and Beebe,⁵ in an article published in 1909, furnished cogent arguments against the "calcium deficiency" theory and in favour of the symptoms being due to accumulation of some toxic agent in the blood.⁶

In man cataract is often found to be associated with chronic tetany; it has further been described in parathyroidectomised dogs and rats.⁷ This also has been supposed to be due to deficiency of calcium. It is, however, of interest to note that the coagulation time of the blood is not altered in tetania thyreopriva.⁸

There seems to be no doubt that the administration of calcium—especially in the form of calcium lactate—tends to cause amelioration of the nervous symptoms of tetania parathyreopriva⁹ and also of tetania infantum. According to Marine and Lenhart,¹⁰ a permanently beneficial result is only obtained if there is some parathyroid tissue left.

Causation of the Nervous Symptoms in Tetany.—It has frequently been suggested that the nervous symptoms of tetania thyreopriva, since they occur most markedly in carnivora, are induced by the accumulation in the blood of certain products of protein metabolism. One such product is guanidine or methyl-guanidine, which has been shown by Noël Paton and Findlay and their fellow-workers, A. Watson, W. A. Burns, J. S. Sharpe, and G. M. Wishart,¹¹ to occur in amounts considerably above normal in the blood of parathyroidectomised animals (6 to 16 mgm. instead of 1 mgm.) as well as in their urine (twice the normal amount). A similar excess has been noted in children afflicted with idiopathic tetany—due, as we have seen, probably to atrophy of

¹ *Arch. f. exper. Path. u. Pharm.*, lxxix., 1921. The literature of the subject will be found in this paper.

² *Journ. Exper. Med.*, xi., 1909. F. S. Hammett (*Journ. Biol. Chem.*, lvii., 1923) noticed a deficiency of Ca in the ash of bones of (female) parathyroidectomised rats.

³ *Ibid.*, xviii., 1913.

⁴ *Ber. u. d. ges. Physiol.*, ii., 1920.

⁵ *Journ. Med. Res.*, xx., 1909. See also J. V. Cooke, *Journ. Exper. Med.*, xii., 1910.

⁶ The subject is more fully discussed by Sutherland Simpson in *Endocrinology and Metabolism* (op. cit.).

⁷ W. Edmunds, *The Ophthalmoscope*, xiv., 1916; Hayano, *Nippon Ganka Gakkai*, 1920.

⁸ S. Simpson and Rasmussen, *Quart. Journ. Exper. Physiol.*, x., 1916.

⁹ Luckhardt and Goldberg (*Journ. Amer. Med. Assoc.*, lxxx., 1923) state that "massive" doses of calcium lactate will keep parathyroidectomised dogs free from tetany; which at once comes on if the doses are intermitted.

¹⁰ *Arch. intern. Med.*, vii., 1911, and *Journ. Exper. Med.*, xix., 1914.

¹¹ *Quart. Journ. Exper. Physiol.*, x., 1917.

parathyroids—as compared with normal individuals of the same age. The metabolic disturbances produced by guanidine poisoning are also similar to those of parathyroidectomy. The above-named observers have found that injections of guanidine and methyl-guanidine produce in rabbits, cats, and rats symptoms similar to those resulting from parathyroidectomy, viz. muscular tremors (fig. 46), spastic rigidity, hyperexcitability of peripheral nerves and muscles, acidosis with retention of phosphorus, diminution of calcium and of glucose in blood and changes in the N-metabolism. The assimilation of glucose is interfered with, and alimentary glycosuria is readily produced. The liver

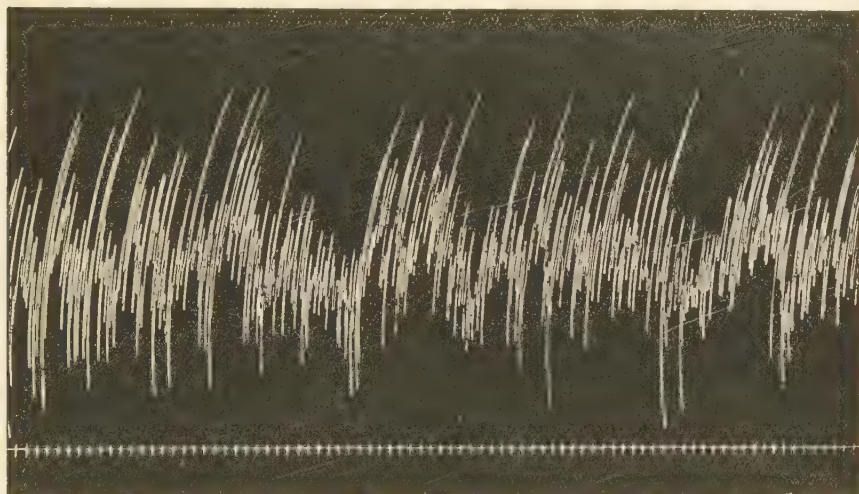


FIG. 46.—Tracing of tremors and jerkings of hind-limb of cat after administration of guanidine hydrochloride. Time in seconds. Compare with fig. 43. (Noël Paton and Findlay.) The spinal cord had been cut.

glycogen disappears.¹ The serum of the blood of parathyroidectomised animals has an influence upon the nerve-muscle preparation of the frog similar to that of dilute solutions of guanidine and methyl-guanidine, in both cases twitchings of the muscles being caused,² although less constantly with the serum than with guanidine solutions. The above-mentioned authors conclude that the symptoms of tetania thyreopriva are produced by the accumulation of guanidine—which is a product of protein metabolism—in the blood, owing to inability on the part of the organism deprived of parathyroids to complete its metabolism and convert it into a non-toxic substance. If this, as appears most probable, is the case, it indicates that the parathyroids

¹ Underhill and Blatherwick, *Journ. Biol. Chem.*, xviii., 1914.

² G. M. Wishart, *Quart. Journ. Exper. Physiol.*, x., 1917. B. A. Houssay (*ibid.*, xii., 1919) obtained such twitchings in toad muscle, just as often in the serum of normal dogs as in those with tetany, and altogether failed to obtain them with the muscles of the South American frog (*Leptodactylus ocellatus*). Yoshimoto (*Quart. Journ. Exper. Physiol.*, xii., 1922) confirms the fact that guanidine has the same effect as parathyroidectomy in increasing the excitability of the nerve-muscle preparation of the frog (*Rana temporaria*).

pass into the blood an autacoid (which we may provisionally term *parathyrin*), which assists in promoting protein metabolism and enables intermediate products such as guanidine to be further metabolised. Such an autacoid may be conceived to play the part of a complement in the sense used by Ehrlich, linking up the guanidine molecule with the protoplasm of the cells within which protein metabolism is effected; its absence from the blood would result in the accumulation of guanidine to an extent capable of producing toxic effects. An alternative to this hypothesis is that the autacoid may act as a direct chemical antagonist to guanidine in the blood (see Vines, p. 86). To suppose that the chemical change, whatever it may be, goes on in the parathyroids themselves, the guanidine being conveyed to them by the circulating blood and undergoing transformation in their substance is improbable in view of the minute size of these organs and the very small proportion of the total blood which can flow through them.

We must not lose sight of the fact that a minute amount of guanidine may be useful in the organism: it is its accumulation which is to be avoided. Noël Paton and Findlay suggest that the tonus of skeletal muscle may in part be regulated by guanidine in the blood.

Both after parathyroidectomy (cat) in absence of tetany, and also in poisoning by guanidine, the irritability of the cardiac vagus is diminished: the administration of calcium lactate can again increase it.¹

A large number of experiments upon the effects of guanidine and di-methyl-guanidine poisoning on various animals by Frank, Stern, and Nothmann² show that the symptoms produced are singularly like those met with in idiopathic tetany, although minor differences were observed.

Historical.—Verstraeten and Vanderlinden³ noticed that the tetany following parathyroidectomy was more violent and appeared sooner after the operation if the animals were kept on a meat diet, and suggested that the function of the parathyroids is in some manner connected with the metabolism of protein.⁴ Morel regarded the glands as serving for the destruction of certain toxic substances which would produce tetany if allowed to accumulate in the blood.⁵

W. F. Koch⁶ first described the occurrence of toxic bases such as methyl-guanidine in the urine of parathyroidectomised dogs, and suggested that this and similar products might cause the symptoms of tetany. This observation of Koch was confirmed by Burns and Sharpe, and by them extended to the blood.⁷ Findlay and Sharpe obtained the same results in a case of idiopathic tetany.⁸

¹ Burns and Watson, *Journ. Physiol.*, lii., 1919. The same authors state that guanidine increases the action of adrenaline upon the blood-vessels and uterus (*Proc. Physiol. Soc.*, *ibid.*, liii., 1920).

² *Zeitschr. f. exper. Med.*, xxiv., 1921.

³ *Mém. cour. Acad. roy. de méd. de Belgique*, xiii., 1894. See also Cooke, *Journ. Exper. Med.*, xiii., 1911.

⁴ According to Hammett, the poison which causes tetany is derived from endogenous metabolic changes and not from proteins of the food (*Amer. Journ. Physiol.*, lxiii., 1922).

⁵ *Les parathyroïdes*, Paris, 1912; *Presse méd.*, 1913.

⁶ *Journ. Biol. Chem.*, xii., 1912; xv., 1913.

⁷ *Quart. Journ. Exper. Physiol.*, x., 1916.

⁸ *Quart. Journ. Med.*, xiii., 1920.

P. S. Henderson¹ found guanidine in the muscles in parathyroidectomised animals. Since guanidine is deacetylated creatin, and, as Henderson suggests, probably forms a stage in the formation of creatin, this is perhaps the transformation which is produced under the influence of the autacoid formed by the parathyroid. In confirmation of this view Wishart obtained an increase of creatin in the muscles of animals to which guanidine had been administered.²

It has also been found that after complete thyroidectomy in which the parathyroids were included there is a marked increase in creatin in the excreta.³ It is of interest to note that the parathyroids yield a creatin-splitting ferment.⁴

Idiopathic tetany of children is most frequent from two years to five or six, and occurs up to fifteen years of age.⁵ From two to six years is precisely the period in which creatin occurs normally in the urine,⁶ whereas this substance is absent in very young children, in whom also idiopathic tetany is extremely rare.⁷

The experimental evidence furnished by Noël Paton and his fellow-workers, and already given in full, seems unquestionably to point to the symptoms of tetany being caused by a toxin like guanidine. According to Dragstedt and Peacock,⁸ such a toxin is produced in the intestine, and if treatment is directed to the prevention of its formation, parathyroidectomy does not produce the usual effects.

PHYSIOLOGICAL EFFECTS OF PARATHYROID EXTRACT

Ott stated that parathyroid extracts, when injected intravenously, cause the blood-pressure to be first raised, then lowered, and the rate of respiration to be increased; that they are diuretic, acting directly on the renal epithelium, and that in large doses they have the effect of lowering the body temperature. Also that applied locally the extracts increase the extent of the contraction both of intestines and uterus, and dilate the pupil. These statements have not been confirmed by other observers. I have myself not succeeded in getting the results described by Ott, nor in observing any specific effect of the boiled and filtered extract, and it is now generally agreed that the parathyroid secretion produces no acute effect when injected into the blood.

Cameron and Carmichael⁹ find that feeding with parathyroid has not the effect on the growth of organs of white rats which is produced by feeding with thyroid. It is interesting, in view of the fact that tetany is produced by removal of parathyroids, that several of their animals which were fed with large doses of parathyroid developed tetany.

¹ *Journ. Physiol.*, lii., 1918.

² *Journ. Physiol.*, liii., 1920. See, however, F. S. Hammett, *Journ. Biol. Chem.*, lv., 1923.

³ G. Frontali, *Arch. intern. de physiol.*, xiii., 1913; A. Hunter, *Quart. Journ. Exper. Physiol.*, viii., 1914.

⁴ Gottlieb and Stangassinger (*Zeitschr. f. physiol. Chem.*, lii., 1907) also obtained a strongly acting ferment from a goitrous thyroid (dog).

⁵ W. C. Rose, *Journ. Biol. Chem.*, xxvi., 1916.

⁶ It may, however, continue to be found longer in girls, and may in them last to puberty (R. A. Krause, *Quart. Journ. Exper. Physiol.*, vii., 1913).

⁷ J. S. Sharpe (*Biochem. Journ.*, xiv., 1920) found ten times as much guanidine in the faeces in children with idiopathic tetany as in normal children.

⁸ *Amer. Journ. Physiol.*, lxiv., 1923. See also Dragstedt, Phillips, and Sudan, *ibid.*, lxv., 1923. This contains references to previous papers by the same authors.

⁹ *Amer. Journ. Physiol.*, lviii., 1921, and *Trans. Roy. Soc. Canada*, xvi., 1922.

Feeding with fresh parathyroid appears to have no influence on the development and metamorphosis of tadpoles.¹

THERAPEUTICAL EFFECTS OF PARATHYROID SUBSTANCE

Parathyroid is given as dried substance or fluid extract in affections characterised by increased excitability of the nervous system: especially of the peripheral nerves. It may be administered by the mouth or hypodermically, and should be accompanied by calcium lactate, given orally. H. W. C. Vines has devised a method for standardising preparations of parathyroid by determining their effect in removing guanidin from a standard solution containing it.²

RELATION OF THE PARATHYROIDS WITH OTHER ENDOCRINE ORGANS

With the Thyroid.—Although some authors have thought that the parathyroids can act vicariously for the thyroid, the generally received and most probable opinion seems to be that they are independent in function, or, if anything, antagonistic. They usually show no enlargement in congenital atrophy of the thyroid, and although certain experiments by Vincent and others have appeared to indicate that there may be enlargement and colloid formation after thyroidectomy, it must be borne in mind that it is by no means difficult in experiments of this kind for errors to creep in.³

There seems, however, to be no doubt that some cases of tetany benefit by the administration of thyroid extracts, although the tetany cannot be cured by such administration.

Halpenny and Thompson⁴ state that after parathyroidectomy the vesicles of the thyroid become large and irregular, the gland being apparently more active. There is also a multiplication of the intervesicular cells, the appearance (fig. 47) being not unlike that of the thyroid in cases of exophthalmic goitre (see fig. 21) and of hyperplasia of a "remainder" fragment (fig. 7).

With the Pituitary.—Mrs Thompson described colloid vesicles in the pars intermedia of the pituitary after parathyroidectomy, and concluded that this is a vicarious effect; but it must be remembered that there are great individual variations in the number of such vesicles in the pituitary, and that some animals exhibit a large number even normally. Most other authors have failed to substantiate any change in the pituitary after parathyroidectomy alone, although there are marked changes after thyroidectomy.

With the Suprarenals.—Very little that is definite has been substantiated regarding the relations of the parathyroids with the suprarenal capsules. It has, however, been affirmed that removal of the suprarenals prevents the appearance of tetany after parathyroidectomy; but only when the thyroid is included in the removal. On the other hand, it is stated that adrenaline

¹ W. Schultze, *Arch. f. Entwicklungsmech.*, xlviii., 1921.

² *Brit. Med. Journ.*, ii., 1923, p. 359.

³ Vincent has himself now given up the idea that these organs have a common function (*The Ductless Glands*, 2nd edition).

⁴ *Anat. Anz.*, xxxiv., 1909.

injection will bring on a fit of tetany in a parathyroidectomised animal.¹ These effects point to a certain antagonism between suprarenal and parathyroid, but they must be produced through the nervous system.

Hammett² found that removal of parathyroids in the rat—not including the thyroids—is followed by a marked increase in the size of the submaxillary glands.

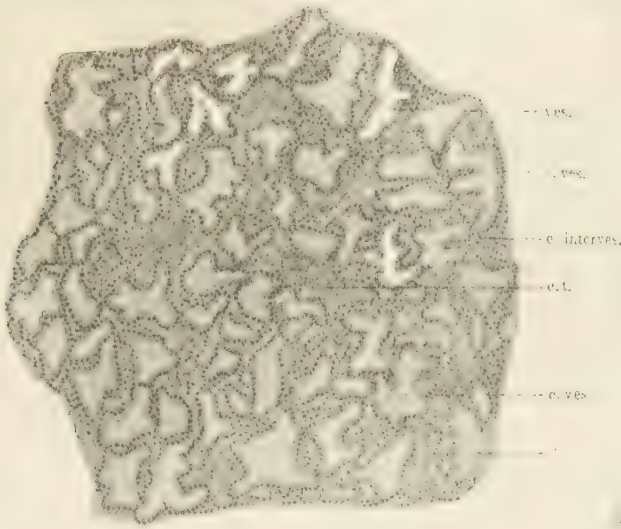


FIG. 47.—Section of thyroid of dog 32 days after removal of all the parathyroids. (Halpenny and Thompson.)

ves., vesicle; e. ves., epithelium lining vesicle; e. interves., intervesicular tissue; c.t., connective tissue.

C. Artoni³ got diminution in the amount of enteric juice secreted, as well as of its digestive activity.

Peacock and Dragstedt⁴ got no effect on gastric secretion from complete thyroparathyroidectomy, provided tetany were prevented by controlling the diet.

With other Organs.—Gozzi⁵ has described degenerative changes in the liver cells as a result of parathyroidectomy, but regards them as secondary to the general effects on the organism as a whole.

¹ Guleke, *Arch. klin. Chir.*, xciv., 1911.

² *Amer. Journ. Anat.*, xxxi., 1922.

³ *Arch. di fisiol.*, xx., 1922.

⁴ *Amer. Journ. Physiol.*, lxiv., 1923.

⁵ *Internat. Monatschr. f. Anat. u. Physiol.*, xxix., 1912.

CHAPTER X

THE SUPRARENAL CAPSULES

STRUCTURE

THE suprarenal capsules (adrenals) in man lie in contact with and immediately above each kidney. Shaped somewhat like a cocked hat, each has a hilum on the ventral surface (fig. 48): from this the chief suprarenal vein emerges (fig. 49). The gland is enclosed by a connective-tissue capsule which is continuous with the connective tissue of the gland. The left gland is usually the larger. The right gland is closely applied to the inferior vena cava.



FIG. 48.—Ventral view of right kidney and suprarenal capsule of full-grown foetus. (Allen Thomson.)

r., kidney (lobulated in foetus); *v.*, renal vessels; *u.*, ureter; *s.*, suprarenal capsule, showing hilum; *v'*, suprarenal vein formed by tributaries from the surface vessels joining the main vessel, which is emerging from the hilum.

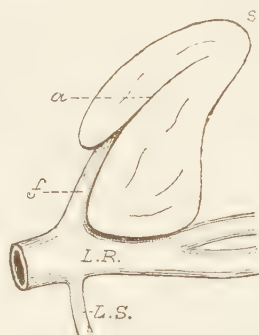


FIG. 49.—Outline of left suprarenal capsule showing its chief vein emerging from the hilum. (Symington, after Rolleston.)

s., apex of capsule; *d.*, hilum; *f.*, suprarenal vein, joining, L.R., left renal vein; L.S., left spermatic vein.

The average dimensions of each in man are: height 27 mm., breadth 47.5 mm., thickness 4.5 mm. (except at the base, where they are about twice this amount). They are usually larger in the female than in the male. Together they weigh 8.5 to 10 grams: but they exhibit considerable variation in size and weight.

P. T. Herring¹ finds that in the young female white rat the suprarenals are 40 per cent. heavier than in the male, and that the adrenaline content of the

¹ *Quart. Journ. Exper. Physiol.*, xii., 1919. The suprarenal capsules are much larger in the (active) wild Norway rat than in the relatively inactive albino, irrespective of sex (Hatai, *Anat. Record*, viii., 1914).

female is more than twice as great as that of the male of the same size. The weight is increased during pregnancy. Thyroid feeding produces a rapid increase : this is more marked in the male than in the female, and mainly affects the cortex, so that the percentage amount of adrenaline in the organ is diminished.

Each suprarenal consists of two parts, *cortex* and *medulla* (figs. 50, 51), which, although anatomically united in most vertebrate animals, are morphologically distinct and are developed from different embryonic formations ; the cortex being formed from mesoderm-cells of the genital ridge, whilst the



FIG. 50.—Section through middle of suprarenal capsule of foetus. (Allen Thomson.) Twice the natural size.

r., kidney ; *v.*, suprarenal vein issuing from hilum.

In a section through the middle the medulla appears thicker than the cortex, but towards the sides the cortex is much the thicker.

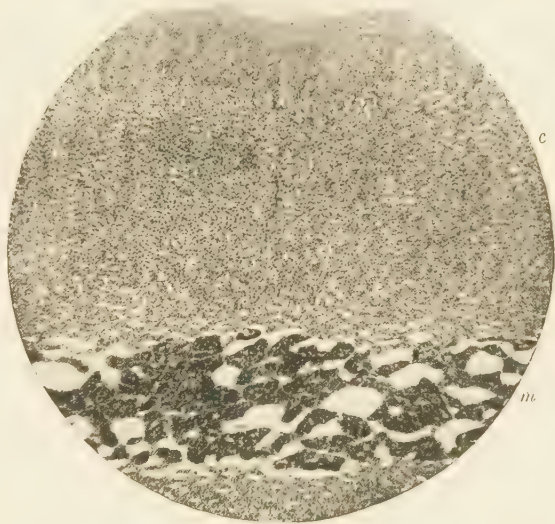


FIG. 51.—Section of suprarenal, low power.
c., cortex ; *m.*, medulla.

medulla is developed from cells which belong to the same neuroblast-masses as give rise to the nerve-cells of the sympathetic ganglia.¹ The cells of the medulla are characterised by the brownish-yellow colour which their granules strike with chromic acid and its salts (chromaphil reaction). This reaction is due to the presence of adrenaline (see p. 110).

In elasmobranch fishes (fig. 52) these two parts remain separate, the cortex being represented by the *interrenal body* and the medulla by the *paired bodies*, which lie close to the ganglia of the sympathetic chain. In higher vertebrates the two parts are united into one organ, which is loosely attached to the kidney. In birds and reptiles and amphibians the renal and adrenal tissues interlock. It is only in mammals that the same condition is found as in man, viz. a central medulla with an enclosing cortex.

Accessory suprarenals are not infrequent. They consist either of cortical substance alone or of medullary substance alone, or of the two combined.

¹ For an account of the growth and formation of the suprarenal capsules (medulla and cortex) of the guinea-pig, and their volumetric relations to one another at different periods of foetal and post-uterine life, see L. Castaldi, in *Arch. di fisiol.*, xx., 1922.

They occur most commonly between the kidneys and along the lower part of the abdominal aorta as far as its bifurcation (figs. 53, 54), but they also extend

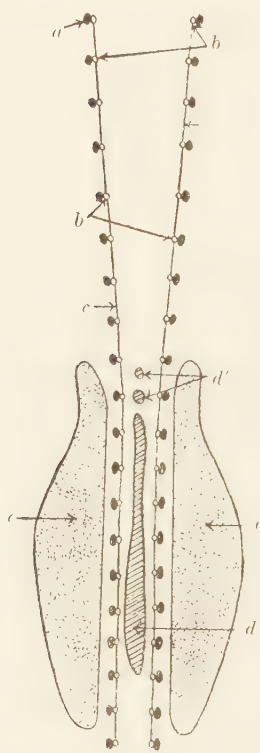


FIG. 52.—Diagram of the suprarenal apparatus of an elasmobranch fish. (Swale Vincent.)

a, paired chromaphil bodies (medullary substance) attached to, b, sympathetic ganglia; c, sympathetic chain; d, interrenal body (cortical substance); d', accessory interrenals; e, e, kidneys.

into the pelvis, occurring in the broad ligament of the uterus in the female and in close relation to the testicle in the male.¹ In the male rat an accessory gland is almost constantly seen close to the epididymis. In a single unusual case an accessory suprarenal has been found within the cranium.² They are relatively larger and more frequent in the newly born than in the adult, in which they may be missed altogether. The possibility of their presence must be borne in mind when considering the results of the extirpation of the adrenals in animals.

Those accessory glands, which have a structure and derivation similar to the medulla of the suprarenal capsules, also contain cells which are coloured brown by chromic acid (fig. 55). Such bodies have been termed *paraganglia* by Kahn, *chromaphil bodies* by Vincent, *chromaffin bodies* by other authors.³

The carotid gland is of this nature.⁴ The coccygeal gland has been stated also to contain chromaphil cells, but this is denied by Stoerk.⁵ Paraganglia invariably occur in close morphological and developmental connexion with sympathetic nerves and ganglia.⁶

Chromaphil cells have been found in almost all vertebrates, even in *Petromyzon*.⁷ They have also been described in the epithelium cells of the mantle of a gasteropod (*Purpura lapillus*).⁸ In annelids they occur in some of the nerve-cells of the segmental ganglia.⁹ This is well seen in the leech, the blood-vessels of which react to adrenaline like those of vertebrates.¹⁰ The development of chromaphil cells is, according to J. F.

¹ A. Kohn, *Arch. f. mikr. Anat.*, liii., 1899; and lxii., 1903.

² R. Meyer, *Virchow's Archiv*, ccx., 1912.

³ On the anatomy and physiology of the paraganglia, see R. H. Kahn, in *Arch. f. d. ges. Physiol.*, cxlvii., 1912. Kahn has shown that the abdominal paraganglia of the dog contain adrenaline.

⁴ P. Mulon, *Arch. gén. de méd.*, 1904.

⁵ *Arch. f. mikr. Anat.*, lxix., 1906.

⁶ H. Stilling, *Anat. Anz.*, xv., 1899; E. Giacomini, *Monit. zool. ital.*, xiii., 1902, and xv., 1904.

⁷ J. F. Gaskell, *Journ. Physiol.*, xlv., 1912.

⁸ H. E. Roaf, *Quart. Journ. Exper. Physiol.*, iv., 1911.

⁹ Poll and Sommet, *Verhandl. d. physiol. Gesellsch.*, *Arch. d. Physiol.*, 1903.

¹⁰ J. F. Gaskell, *Proc. Roy. Soc.*, 1914.

Gaskell, correlated with that of a muscular vascular system. He has further shown that the annelid heart reacts to adrenaline in the same way as the vertebrate heart.¹

Abel and Macht² have made the interesting observation that certain patches

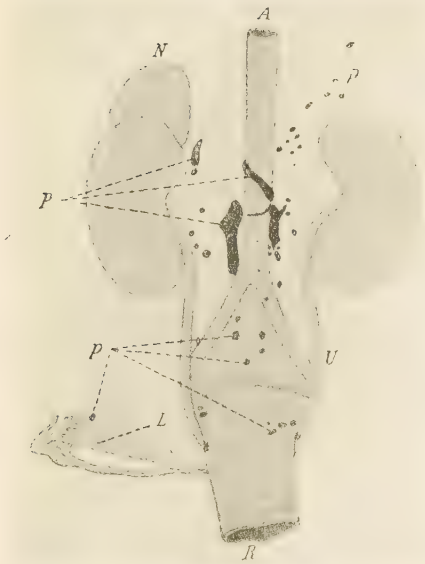


FIG. 53.—Accessory suprarenals or paraganglia in human foetus. (A. Kohn.) The diagram shows the most common situations where such accessory suprarenals occur in mammals.

N., suprarenal; *A.*, aorta; *R.*, rectum; *U.*, ureter; *L.*, ovary; *p.*, paraganglia.

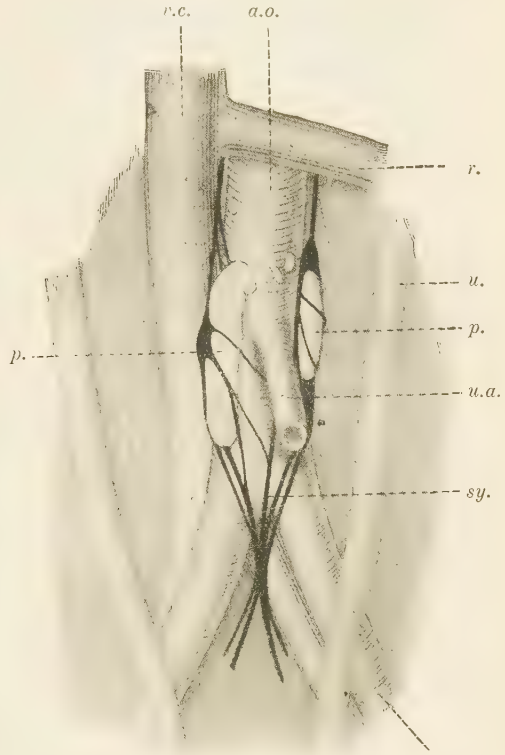


FIG. 54.—Dissection of lower end of aorta and adjacent structures in human foetus, showing the accessory suprarenals or paraganglia usually present. (Zuckerkandl.)

ao., aorta; *v.c.*, vena cava; *r.*, renal vein; *u.*, ureter; *u.a.*, umbilical artery; *sy.*, sympathetic plexus; *pp.*, paraganglia aortica.

of skin glands on the head of a large American toad (*Bufo aqua*) furnish a white, pasty secretion containing a considerable proportion of adrenaline (about 5 per cent.).

STRUCTURE OF THE CORTEX

The cortex of the suprarenal (fig. 56) is composed of polygonal epithelium cells arranged mainly in columns (*zona fasciculata*), but near the medulla as a network of trabeculae (*zona reticularis*). Towards the surface the cell-columns end in rounded and sometimes hollow terminations forming the so-called *zona glomeru-*

¹ *Journ. Physiol.*, liii., 1919; *Journ. Gen. Physiol.*, ii., 1919.

² *Journ. Pharm. and Exper. Therap.*, iii., 1912.

losa, the cells of which, in some animals, tend to have a columnar form. Those of the *zona fasciculata* are usually larger than in the other parts. The cells of the cortex are often described as *clear* and *dark*, according to their staining with iron-haematoxylin. This may, however, be due to functional changes in the same kind of cell. The cells contain typical mitochondria.¹ Characteristic of the cortical cells is the presence of lipid granules and a lipochrome which imparts a yellowish colour to this portion of the capsule.² The lipid granules are said to be formed from the mitochondria.³ The *zona reticularis* contains

pigment granules as well; in the guinea-pig these give it a brownish colour.

The human foetus has unusually large suprarenal capsules. It has been shown that this is almost entirely due to a great development of an innermost part of the cortex lying at the boundary with the medulla (*boundary zone* of Elliott and Armour⁴ (fig. 57): this layer is very vascular. It is not to be confounded with the *intermediate zone* of Virchow, a very thin layer, pigmented in old age, lying at the junction of cortex and medulla. The cells of the boundary zone differ from those of the rest of the cortex in having no lipid granules. After birth they undergo a fatty change and the layer gradually disappears, so that it is no longer distinguishable after the first year. At birth what will be the cortex of the adult gland consists only of a thin peripheral layer of cells containing lipoids; these cells

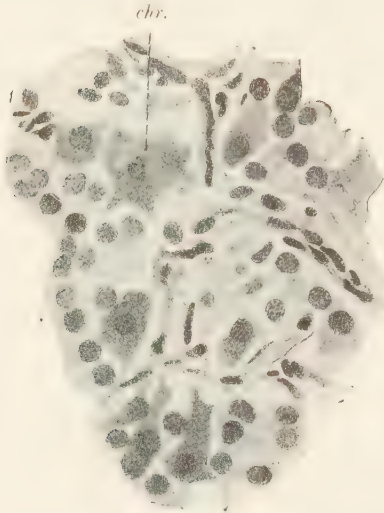


FIG. 55.—Section from an accessory suprarenal or paraganglion of a newborn child. (Zuckerandl.)

chr., a chromophil cell.

multiply, and the layer enlarges *pari passu* with the disappearance of the boundary zone. A remarkable fact pointed out by Elliott and Armour is that in the anencephalous foetus the boundary zone is absent and the suprarenal resembles that of other foetal mammals.⁵

In the cells of the cortex nearest to the medulla fine granules, staining black with osmic and insoluble in turpentine, are seen. These resemble in appearance and reaction the adrenaline-containing granules within the cells of the medulla.⁶

Enlargement of the suprarenal capsules—mainly of the cortex—has been

¹ Mulon, *op. cit.*

² For further details regarding the lipoids of the cortex, see pp. 106 to 108.

³ C. Da Costa, *Arch. de biol.*, xxviii., 1913.

⁴ *Journ. Path. and Bact.*, xv., 1911.

⁵ R. Meyer (*Deutsch. Arch. kl. Med.*, cxxxvii., 1921) finds great variation in the suprarenals in anencephaly. They may be normal, are frequently atrophied, and the medulla is often hypertrophied.

⁶ W. Cramer, *Proc. Physiol. Soc., Journ. Physiol.*, lii., 1918. F. A. and W. E. Hastman (*Amer. Journ. Physiol.*, lxx., 1923) state that they can get physiological evidence of adrenaline (inhibition of intestines) in shavings of frozen cortex containing no medulla. Completely negative results were obtained by Oliver and Schafer (*Journ. Physiol.*, xviii., 1895) on blood-pressure, from extracts of such shavings.

frequently noted in infection and as the result of inoculation with disease toxins.¹ And although thyroid feeding seems unquestionably to produce enlargement of the suprarenal capsules, the removal of the thyroid has been also found to be associated with their hypertrophy.² It is possible that in the one case the medulla, in the other the cortex, is more involved in the change; but, as the organs cannot be separated into the two parts for weighing, this point is not easy of determination. It is stated that deficiency of the antiscorbutic vitamin tends to enlargement of the suprarenal capsules, and that this also occurs in pigeons affected with experimental beriberi by feeding with polished rice. The enlargement is accompanied by increase in adrenaline-content. In connexion with this circumstance it may be mentioned that deprivation of food has a similar effect in causing enlargement of the suprarenals and increase of their adrenaline-content.³

STRUCTURE OF THE MEDULLA

The medulla is composed of cells which have a different form and structural appearance from those of the cortex. They are arranged in what appear in section like irregular anastomosing columns with large blood-spaces between. But, in point of fact, the medulla is better described as a solid cell-mass permeated by sinus-like blood-vessels (figs. 51, 58) with the cells compactly arranged between and around them. The cells of the medulla are irregularly polygonal in form, but where they abut on the sinuses they often assume a more columnar aspect. There can be little doubt that the materials they secrete find their way directly into the blood within the blood-spaces. The cell-proto-

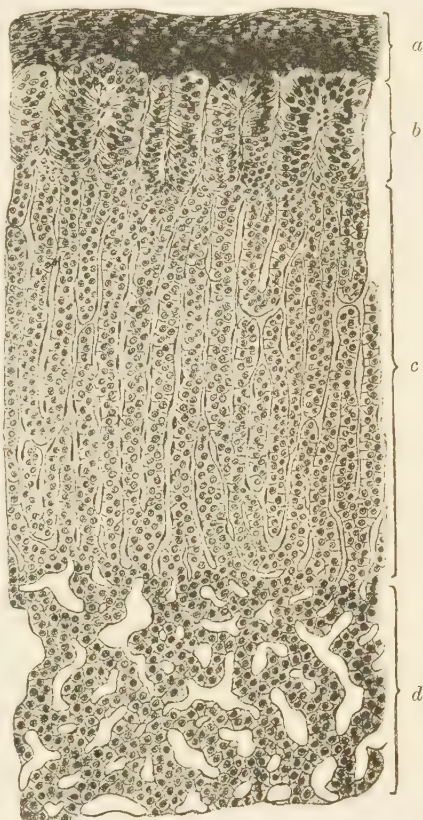


FIG. 56.—Section of cortex of suprarenal : dog. (Böhm and Davidoff.)

a, fibrous covering ; *b*, zona glomerulosa ; *c*, zona fasciculata ; *d*, zona reticularis.

¹ J. Langlois, *Arch. de Physiol.*, 1897 ; Mulon and Porak, *C. r. soc. biol.*, lxxvii., 1914 Porak, *Journ. de Physiol.*, 1919.

² E. Gley, *Arch. internat. de physiol.*, xiv., 1914 ; Carlson, *Journ. Amer. Med. Assoc.*, lxxvii., 1916 ; Stewart and Rogoff, *Amer. Journ. Physiol.*, lvi., 1921.

³ R. M'Carrison, *Ind. Journ. Med. Res.*, 1919, and *Proc. Roy. Soc.*, xci., 1920 (pigeons). See also C. H. Kellaway, *ibid.*, xcii., 1920, and Vincent and Hollenberg, *Endocrinology*, iv., 1920 (rat, dog). C. H. Byrne (*Brit. Med. Journ.*, ii., 1919) found enlargement, mainly of the cortex, in soldiers who had died in prison camps where the food-supply was deficient.

plasm contains chromaphil granules¹ which vary in size and amount in different cells (Carlier). These cells are stained brown with chromic acid and its salts (adrenaline or chromaphil reaction). Similar reactions are sometimes obtained in the blood- and lymph-vessels of the medulla in sections of the organ. The blood in the sinuses may also give the green reaction with ferric chloride which is characteristic of adrenaline (p. 111).²

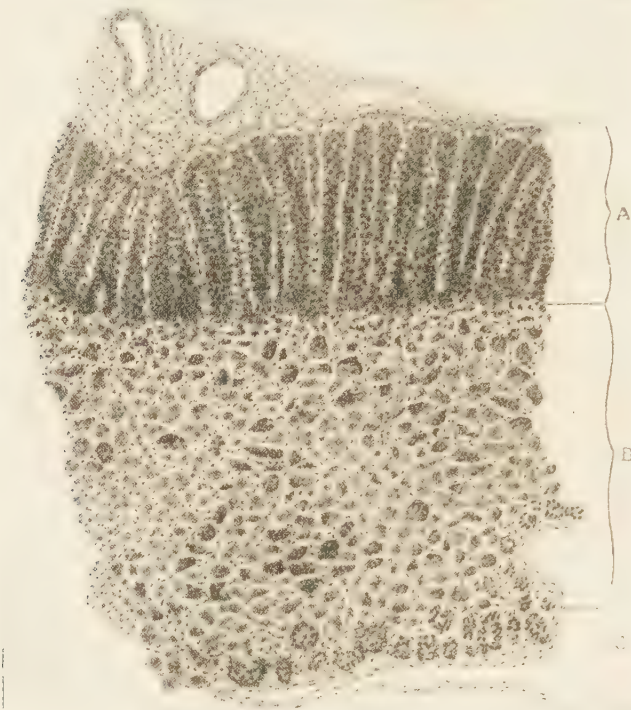


FIG. 57.—Section of suprarenal of child 12 days old, low power. (Elliott and Armour.)

A, outer part of cortex : B, large cells forming boundary zone of cortex ; C, thin layer of medulla : just below is the central vein.

Besides the chromaphil granules above mentioned others are found, somewhat coarser, soluble in water and alcohol but not in ether, and staining with difficulty. Lipoid and pigment granules may also occur. The relationship of these various granules to one another is not known.³

¹ The chromaphil granules within the cells can be well shown by exposing thin slices of the gland to the vapour of osmic acid for 1½ hours at a temperature of 37° C. (W. Cramer, *op. cit.*). The effects upon the number and amount of these (adrenaline) granules of various experimental conditions—such as thyroid feeding and thyroidectomy, exposure to cold and fever, hæmorrhage, drugs, nerve stimulation—are given by Cramer in the Report of the Imperial Cancer Research Fund for 1919.

² For other ways of staining the granules in the cells of the medulla, see B. F. Kingsbury, *Anat. Record*, v., 1911.

³ For observations on the microscopic structure and development of the suprarenal bodies in various species, see G. Trinci, *Arch. ital. d. Anat. e d. embriol.*, xiv., 1916.

VESSELS AND NERVES OF THE SUPRARENALS

*Blood-supply.*¹—The blood-vessels are very numerous. The arteries, three in number—derived from the inferior phrenic, the aorta, and the renal artery respectively—enter at the surface and give off branches to supply the cortex with a rich capillary network. The blood-vessels do not penetrate the cell-columns of the zona glomerulosa and zona fasciculata of the cortex, but form a network round them. The walls of the capillaries are said to be so far incomplete as to permit fine particles to pass through them.² In the zona reticularis the vessels become larger, take on a sinus-like character, and come

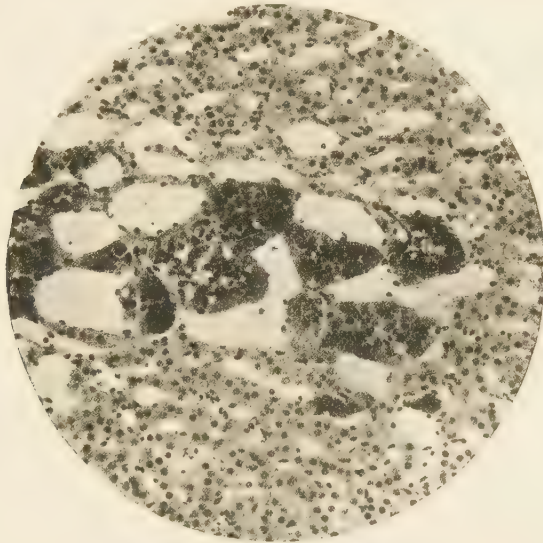


FIG. 58.—Section of suprarenal at thin part of medulla. Magnified 150 diameters. In this section as well as in that shown in fig. 51 the cells of the medulla are darkly stained. They contrast strongly with the cells of the zona reticularis of the cortex. The blood-sinuses of the medulla are seen to be continuous with those of the zona reticularis.

into close relationship to the cells. They are continuous with the venous sinuses of the medulla. E. Luna³ states that the veins of the organ are derived from the cardinal vein of the embryo as sinus-like outgrowths, with only endothelial cells separating them from the cells of the medulla. The arteries grow later into the cortex and open into the sinuses of the zona reticulata by capillary vessels which pass down between the columns of the zona fasciculata. The larger veins of the suprarenal medulla are surrounded by longitudinally disposed plain muscle-fibres. A few arterioles are said to pass directly to the medulla from the capsule of the organ. The suprarenal vein of the right side enters the inferior vena cava either directly or along with one of the lumbar veins: that of the left side usually joins the corresponding renal vein (fig. 49).

¹ J. M. Flint, *Johns Hopkins Hosp. Rep.*, ix., 1900.

² L. Felicini, *Arch. f. mikr. Anat.*, lxiii., 1903.

³ *Internat. Monatschr. f. Anat. u. Physiol.*, xxvii., 1910.

The blood is conveyed away from the gland for the most part by the vein which leaves it at the hilum. There is also a venous plexus surrounding the capsule of the gland, which communicates with a similar plexus around the kidney,¹ and there may also be some communication with veins of the diaphragm.²

According to Neumann the blood-supply of the suprarenal is more abundant than that of any other organ in the body,³ viz. as much as 6 to 7 c.c. per gram and per minute (with a blood-pressure of 130 mm. Hg). This is even higher than that of the thyroid, which comes next with 5 c.c. per gram and per minute. The respiratory exchange is also very high (0.045 c.c. to 0.06 c.c. oxygen per gram per minute).⁴

In birds and reptiles the suprarenals have a venous blood-supply as well as an arterial—blood being conveyed to each gland by a “portal” vein which is usually formed by the junction of two or three intercostal veins.

The connective-tissue septa of the cortex contain lymphatics, which communicate directly with lymph-vessels in the medulla. There is a subcapsular network of lymph-vessels which communicates with glands along the aorta and also with glands in the posterior mediastinum.

Nerve-supply.—The suprarenals are very richly supplied with nerves. Each receives no less than thirty-three nervous filaments (Kölliker), derived from the greater splanchnic through the suprarenal plexus, which is itself constituted by branches from the celiac, phrenic, and renal plexuses.⁵ After forming a network in the connective-tissue investment of the organ, the nerves penetrate into the cortex, partly supplying its blood-vessels, partly its cell-columns. Most of the nerves extend to the medulla, where they form a plexus from which filaments pass to end between the cells. Groups of sympathetic nerve-cells are stated to be occasionally found both in the medulla and in the deeper parts of the cortex. But according to T. R. Elliott⁶ there are usually no ganglion cells in the medulla, the cells of which are the morphological equivalent of sympathetic ganglion cells. He finds that after section of

¹ Tuffier and Lejars, *Arch. de Physiol.*, 1891; G. M. Flint., *op. cit.*; D. Cow, *Journ. Physiol.*, xlviii., 1914.

² Gley and Quinquaud, *Journ. de physiol.*, xix., 1921.

³ The pituitary (*pars anterior*) must probably be excepted.

⁴ K. O. Neumann, *Journ. Physiol.*, xliii., 1911, and xlv., 1912. Burton-Opitz and Edwards (*Amer. Journ. Physiol.*, xliii., 1917), and Stewart and Rogoff (*ibid.*, xlv., 1917), obtained a somewhat lower figure for the rate of flow, but the blood-pressure was lower in their experiments. Burton-Opitz and Edwards found a rather lower rate for the suprarenals than for the thyroid, but in both it was very high in comparison with other vascular organs such as the kidney. See R. Burton-Opitz, in *Quart. Journ. Exper. Physiol.*, iv., 1911. The subject has also been investigated by Langlois, Tschoboksaroff, and Gley and Quinquaud, who all obtained somewhat lower results with peptone or hirudin blood, and by Boncompte, in Gley's laboratory, using chloralosed dogs. The last-named observer got a rate of flow of from 3 to 4 c.c. during rest, rising to 5 or 6 c.c. when the splanchnic was stimulated (*C. r. soc. biol.*, lxxxiii., 1920).

⁵ Kahn has shown that while the left suprarenal is only innervated from the corresponding splanchnic, the right suprarenal receives fibres from the splanchnics of both sides.

⁶ *Journ. Physiol.*, xlv., 1913.

the splanchnics the fine myelinated fibres to the suprarenals undergo degeneration right to their endings in the medulla. These are, therefore, preganglionic nerves in the sense of Langley, and there are in all probability no postganglionic nerves.

In connexion with this question it is found that nicotine, which stimulates sympathetic ganglion cells and when injected into a vein increases the amount of adrenaline secreted into the blood, will produce the same effect after the splanchnics have been cut and allowed to degenerate.¹ Under these circumstances it must directly stimulate the cells of the medulla.

¹ F. Eichholtz, *Arch. f. exp. Path. u. Pharm.*, xcix., 1923.

CHAPTER XI
THE SUPRARENAL CAPSULES (*continued*)

DESTRUCTION BY DISEASE

THE suprarenal capsules have received special attention, both from clinicians and physiologists, since Thomas Addison, of Guy's Hospital, described the



FIG. 59.—Thomas Addison (1793–1860). (From a photograph.)

symptoms of the somewhat rare disease which bears his name, and which he associated with degeneration of these organs.¹ Addison's disease is characterised by great languor and general debility, with weakness and diminution

¹ "On the Constitutional and Local Effects of Disease of the Suprarenal Capsules," London, 1855. The history of the subject previously to the time of Addison is given by A. Biedl, in *Janus*, 1910.

of tone, not only of the skeletal but also of the vascular and visceral musculature, feeble action of heart, loss of appetite, disturbance of the digestive tract, severe abdominal pain, and eventually extreme emaciation. These symptoms are associated with a peculiar patchy bronzing of the skin. The body temperature is usually subnormal. Anæmia, which is an occasional accompaniment of the disease, was regarded by Addison, when it occurs, as symptomatic; but it is probably the result not of the destruction of the capsules, but of the intercurrent affection (generally tuberculosis) which has produced their destruction.

The most striking external characteristic of the disease as described by Addison was undoubtedly the pigmentation of the skin, which occurs as a diffuse coloration upon the face and hands and other exposed parts, and is increased in regions where there is some pigmentation normally present (such as the areolæ of the nipples and the external genital organs) as well as in parts exposed to pressure. It may be found on the mucous membrane of the mouth and on that of the conjunctiva. The pigment is in the cells of the rete mucosum, and is also seen in the leucocytes in the cutis vera of the bronzed areas. Sometimes the bronzing does not occur: these cases are the more acute. The disease is usually fatal within two years.¹ Its course may be prolonged, "even to six or ten years. In rare instances recovery has taken place, and periods of improvement lasting many months may occur" (W. Osler). Some cases are markedly benefited by administration of suprarenal extract *per os* or hypodermically; others not at all.²

The cause of the excessive formation of pigment is not understood, but it has been suggested (by Adami³ and others) that adrenaline may be derived from the same source as the melanin of the skin, and that, if the formation of adrenaline (? from tyrosine) is interfered with, an excess of melanin is formed and deposited in the integument. Meirowsky⁴ states that in portions of skin removed from patients who have died of Addison's disease an increase of pigment occurs as long as five days after death if the pieces are kept in a warm, moist chamber, but that this does not occur in skin from those who have died from other causes. He suggests that a colourless precursor of the melanin is present in the skin, and supposes this to become transformed under the influence of light or a ferment. Somewhat similar observations have been made by Königstein⁵ on the skin of dogs deprived of their suprarenal capsules: but negative results were obtained with rabbits and other rodents. Animals deprived of their suprarenals do not show unusual pigmentation. If therefore the

¹ W. Hale White, *Clin. Journ.*, 1908.

² It is said that the administration of extract by the mouth will cause a rise of blood-pressure in cases of Addison's disease, although in normal individuals no such effect is observable (O. Grünbaum, *Journ. Physiol.*, xxiv., 1899. A. F. Hurst has described a case in which a foetal suprarenal was implanted into the testicle of a patient dying from Addison's disease, resulting in steady and lasting improvement; the blood-pressure rising to 120 mm. Hg and the hæmoglobin to 80 per cent. in ten months. The bronzing of the skin was unaffected (*Brit. Med. Journ.*, Feb. 18, 1922). (See also p. 103.)

³ *The Principles of Pathology*, 1908.

⁴ *Virchow's Arch.*, cxcix, 1910.

⁵ *Münch. med. Woch.*, 1909.

pigmentation is due to the loss of those organs, it must be the result of a very gradual destruction by disease.

C. Neuberg¹ obtained from a sarco-melanoma which was derived from the suprarenal capsule an enzyme which produced a black material when allowed to act on adrenaline. This led him to test an extract from the ink-bag of the cuttle-fish. From this he also got an enzyme (in this case a tyrosinase) which converted adrenaline into "melanin."²

Tests for Suprarenal Deficiency in Man.—Sergent³ has described in various diseases as a symptom indicative of a deficiency in the amount of adrenaline the appearance of a white line as the result of stroking the skin with the fingertip or other blunt object. The part stroked becomes white in about a minute; this lasts two or three minutes, and gradually subsides. Kay and Brock⁴ have investigated this symptom in a large number of cases suffering from various diseases, and also in apparently normal subjects. They conclude that the phenomenon is due to a local vasomotor reflex which has no relation to the activity or non-activity of the suprarenal capsules, and that it does not possess the clinical significance which has been attributed to it.

Another test which has been suggested is that of injecting minute quantities of very dilute solutions of adrenaline (from 1 to 200,000 to 1 to 1,000,000) sub-epidermally. In normal individuals this produces a central blue spot, surrounded by a white halo, and this again by a blue area. The extent of the reaction is said to be diminished in Addison's disease and increased in pregnancy, in conditions of hypertension, and in exophthalmic goitre.⁵

EFFECTS OF SUPRARENAL REMOVAL (EPINEPHRECTOMY: DECAPSULATION)

Addison's account of the disease he described, and which he termed *idiopathic anæmia*, led Brown-Séquard⁶ to test the effect of the removal of the suprarenal glands in animals. The operation, which was performed upon a number of animals of different species (rabbits, guinea-pigs, dogs, and cats), was followed in every case of double extirpation by a fatal termination within thirty-seven hours of the removal. But a fatal result was produced also in all or nearly all the animals in which the lesion was unilateral, although subsequently Brown-Séquard succeeded in keeping some animals alive for a few days when only one capsule was removed. Since it is now well established that careful removal of one capsule under aseptic precautions is not fatal,⁷ there can be little doubt that Brown-Séquard's results were in a considerable measure the consequence of shock and sepsis, and that they could not be

¹ *Bioch. Zeitschr.*, viii., 1908.

² The relation of melanin to adrenaline is dealt with by W. G. Spencer in the "Bradshaw Lecture," *Brit. Med. Journ.*, Nov. 17, 1923. The literature will be found here.

³ *Presse méd.*, xi., 1903; *Endocrinology*, i., 1917; *Presse méd.*, 1921.

⁴ *Amer. Journ. Med. Sci.*, 1921. Samson Wright (*Lancet*, 1922; *Endocrinology*, vi., 1922) and Sezany (*Ann. de méd.*, 1922) come to a similar conclusion.

⁵ Ascoli and Fagioli, *Atti d. r. Acc. d. Lincei*, 1919.

⁶ *C. r. de l'acad. d. sci.*, 1856, 1857.

⁷ An exception must perhaps be made for the guinea-pig, in which unilateral extirpation has been not infrequently followed by death.

relied on as a proof that the suprarenal capsules are essential to life. This is, indeed, the opinion which was formed by many of his contemporaries. Nevertheless, looked at in the light of our present knowledge, it is certain that death must have been either caused or greatly accelerated by the removal of both capsules—since this is now known to be in most animals the invariable result of the double operation, and to occur within a few days.¹ There are exceptions to this in some species of animal: among these the white rat may be particularly mentioned. The exceptions are probably associated with the occurrence of accessory bodies, but whether these must be of cortical or medullary nature—or both—is not fully determined.

The tendency of most experiments is to show that the fatal result of removing the suprarenals is due to the cortex rather than to the medulla. As was first shown by G. Harley,² white rats withstand removal of both capsules without a rapidly fatal result. It is known that these have an unusual number of supplementary capsules, which, according to Swale Vincent, have for the most part the structure of the cortex of the main organs. But although by the macroscopic method of Kohn (brown coloration with potassium bichromate) no chromophil tissue can be demonstrated in the retroperitoneal tissue of the white rat, Falk and Macleod³ obtained strong reactions with uterine and intestinal muscle from this tissue in that animal, as well as the guinea-pig. H. Marti⁴ finds that the male white rat survives decapsulation even after castration, which removes one of the chief accessory organs.

Wheeler and Vincent⁵ removed one suprarenal (in dogs), and attempted to destroy the medulla of the other with the cautery. In several such cases the animals survived, although only cortical substance was found on post-mortem examination.

No effect of the extirpation—especially if the operation is performed on the two glands at an interval of a few days—is at first apparent. For a day or two there is little sign of anything wrong. Presently the animal loses appetite, is less lively, and exhibits signs of muscular weakness. Metabolism is reduced, as evidenced by the gaseous exchanges. The body temperature and heat production become lowered.⁶ The blood sugar is diminished in amount.⁷ The blood-pressure is fairly maintained.

¹ See especially Abelous and Langlois, *C. r. soc. biol.*, 1891 and 1892, and *Arch. de physiol.*, 1892; Hultgren and Andersson, *Skand. Arch. f. Physiol.*, ix., 1899; Strehl and Weiss, *Arch. d. ges. Physiol.*, lxxxvi., 1901.

² *Trans. Path. Soc. London*, ix., 1858.

³ *Amer. Journ. Physiol.*, xl., 1916.

⁴ *Zeitsch. f. Biol.*, lxxvii., 1923.

⁵ *Trans. Roy. Soc. Canada*, xi., 1917. A similar experiment has been made by Houssay and Lewis (*C. r. soc. biol.*, lxxxvii., 1922, and *Amer. Journ. Physiol.*, lxiv., 1923), with the same result. On ablation of the remainder of the capsule the animal dies in from twenty-four to twenty-six hours.

⁶ A. V. Gradinescu, *Arch. f. d. ges. Physiol.*, clii., 1913; T. Gayda (frog), *Arch. d. sci. biol.*, iv., 1923. Marine and Bannerman obtained a contrary result in rabbits (*Journ. Metab. Res.*, ii., 1922), and attribute this to an increase of thyroid secretion. Tsuji (*Acta schol. med. Kyoto*, v., 1923) finds that removal of suprarenals produces hypertrophy of thyroid, like that seen in exophthalmic goitre.

⁷ H. Bierry, *Presse méd.*, 1913.

Trendelenburg¹ found that after removal of both suprarenals in the cat the blood-pressure remained normal for twelve hours or longer, only sinking shortly before death. It was estimated without further operation by Gärtner's method.

R. G. Hoskins² found that after removing in dogs from one-half to seven-tenths of the whole suprarenal tissue the blood-pressure was lowered and its reaction to nicotine was diminished, although its reaction to adrenaline was not affected.

Austmann, Halliday, and Vincent,³ who kept dogs under ether anæsthesia for as long as forty hours after removing both suprarenals, were not able to determine any marked fall in blood-pressure during that time. But the effect seems to depend somewhat on the anæsthetic employed, for Bazett, using urethane instead of ether, found the pressure in the cat to fall in two to three hours.⁴

Dale⁵ found that cats with suprarenals removed, even before they exhibit any obvious symptoms, are very sensitive to the blood-pressure depressing effect of histamine: ten times more so than normal animals. This is a capillary effect. J. T. Lewis⁶ states that rats deprived of suprarenals, although the operation is not fatal and growth, reproduction and glycogenesis remain normal, yet are much more sensitive to toxic substances, such as cobra venom, veratrine, morphine, but not to picrotoxine or strychnine. This passes off after a time. Aub, Forman, and Bright⁷ found a 25 per cent. reduction in the basal metabolism of cats deprived of suprarenals.

Ultimately the muscular weakness becomes extreme, the pulse feeble, the blood-pressure low, and the respiration dyspnœic. Death then soon follows, sometimes immediately preceded by convulsions.⁸ There is little to be seen *post-mortem*, but alterations (vacuolation) have been described in nerve-cells of the cerebral cortex and medulla oblongata.⁹ The pulmonary congestion which has been described is probably the result of respiratory failure.

Decapsulated animals readily become fatigued, and recover very slowly from fatigue.¹⁰ There seems to be an increase of urea in the blood; this may be due to some interference with the functions of the kidneys.¹¹

Moore and Purinton¹² found the longest period of survival in the cat after removal of both suprarenals in two operations to be four days; the shortest less than twenty-four hours. The rhythm of respiration is at first increased; may, in fact, be trebled: later it becomes irregular. Death appears due to respiratory failure, the heart continuing to beat after the respirations have stopped. The

¹ *Zeitschr. f. Biol.*, lxiii., 1914.

² *Ibid.*, xxxvi., 1915.

³ *Trans. Roy. Soc. Canada*, xi., 1917.

⁴ *Journ. Physiol.*, liii., 1920.

⁵ *Harvey Lectures*, 1921.

⁶ *C. r. soc. biol.*, 1921; *Amer. Journ. Physiol.*, lxiv., 1923.

⁷ *Amer. Journ. Physiol.*, lv., 1921.

⁸ T. R. Elliott, *Journ. Physiol.*, xlix., 1914.

⁹ Ettlinger and Nageotte, *C. r. soc. biol.*, xlviii., 1896; E. Donetti, *ibid.*, 1897.

¹⁰ Abelous and P. Langlois suggest that this is due to the accumulation of toxic materials in the blood (*C. r. soc. biol.*, 1891 and 1892). In any case there appears to be a lowered resistance to toxins (E. Boinet, *ibid.*, 1895, 1896, 1897). See also J. T. Lewis, above.

¹¹ Marshall and Davis, *Journ. Pharm. and Exper. Therap.*, viii., 1916.

¹² *Amer. Journ. Physiol.*, iv. and v., 1901.

animal usually dies in a tetanic convulsion. The knee-jerks are greatly exaggerated towards the end. In the goat Moore and Purinton did not always obtain a fatal result, and even if ultimately fatal, the animals survived a relatively long time. Moreover, the convulsive movements noted in the cat were not seen. There was, however, extreme muscular weakness and rapid, shallow respirations. According to Noyons,¹ an animal deprived of its suprarenals is less sensitive to adrenaline than a normal animal, but removal of the pancreas as well as of the suprarenals abolishes this distinction.

Loewi and Gettwert² found that the extirpation of the suprarenals in frogs usually produces a fatal result in about eight days. The heart stops in diastole, but its beating can be made to recommence by the application of atropine. The blood of such animals is poisonous to normal animals, causing inhibition of the heart. The poison is probably choline, most of the physiological properties of which are antagonistic to those of adrenaline.

O. Kosch³ found glycogen to disappear from the liver of rabbits after extirpation of the suprarenal capsules, and the blood sugar to fall gradually. He states that the cholesterol content of the blood is increased, as well as that of the liver. But Stewart and Rogoff⁴ were unable to confirm this. Tying the suprarenal veins is also followed by a fatal result, but after a longer interval than extirpation.⁵

According to Gley and Quinquaud⁶ (in the dog), neither cutting off of the blood-flow from the suprarenals nor their total removal (in the rabbit) has any effect on the excitability of the cardiac nerves, whether sympathetic or vagus.

Addis, Barnett, and Shevky⁷ state that in the rabbit removal of the suprarenals is followed by diminution of urea excretion, whereas subcutaneous injection of adrenaline increases it.

Experiments on adrenal transplantation have for the most part led to negative results.⁸ The graft almost invariably undergoes necrosis and disappears, although some success is said to have been attained by implantation into the kidney and testicle.⁹ Administration of suprarenal extract is unable, either in Addison's disease or in the cachexia produced by extirpation, to prevent the usual fatal termination, although this may be somewhat deferred. The muscular weakness characteristic of Addison's disease may, for a time, tend to disappear with the administration, so that the ergographic record may again approach the normal. But such administration cannot, as in the case of

¹ *IX^{me} Congrès internat. de physiol.*, in *Arch. internat. de physiol.*, xiv., 1913.

² *Arch. f. d. ges. Physiol.*, clviii., 1914. The literature of the subject is given in this paper.

³ *Dissert. Abstr. in Zentrbl. f. Physiol.*, xxx., 1915.

⁴ *Amer. Journ. Physiol.*, xlvi., 1918. Cf. Kuriyama, *Journ. Biol. Chem.*, xxxiv., 1918.

⁵ Hartman and Blatz, *Endocrinology*, iii., 1919.

⁶ *Arch. néerl. de physiol.*, iii., 1918.

⁷ *Amer. Journ. Physiol.*, xlvi., 1918. Cf. Marshall and Davis, *Journ. Pharm. and Exper. Ther.*, viii., 1916.

⁸ E. Boinet, *C. r. soc. biol.*, 1895; Hultgren and Andersson, *op. cit.*; Strehl and Weiss, *op. cit.*

⁹ H. Stilling, *Beitr. z. path. Anat.*, xxxvi., 1905; F. C. Busch, with others, *Amer. Journ. Physiol.*, xv., 1905; *Journ. Amer. Med. Assoc.*, li., 1908; H. Harberer, *Arch. f. klin. Chir.*, lxxvi., 1908, and xciv., 1911; Harberer and Stoerck, *Zeitschr. f. exper. Med.*, vi., 1918.

cachexia thyreopriva, take the place of the internal secretion of the gland, and until measures are found to induce grafts to take in man, Addison's disease will probably continue to terminate fatally. With the progress of surgery the possibility of successful implantation seems less hopeless than was the case only a few years ago.

After extirpation of one gland only there is a compensating hypertrophy of the other, and also of the accessory bodies. Castrated animals were found by Hultgren and Andersson to live much longer after the complete operation than normal individuals. This is also stated to be the case if the complete operation is performed in two stages, first the capsule of the one side and then that of the other being removed. The result is, perhaps, due to the fact that time is thus given for a process of hypertrophy of accessory bodies. With regard to the total amount of suprarenal substance that must remain in order to maintain life, Biedl¹ found in cats, dogs, and rabbits that if one-eighth of the whole suprarenal substance is left the animals always survive. He further found² that if the interrenal body alone is removed in the skate (see p. 89) the animal dies in two or three weeks, becoming progressively weaker and refusing food. In one skate in which a small portion was left these symptoms were absent. In mammals he attempted to destroy the cortex alone: the animals died. It is, however, difficult to believe that the medulla was not seriously injured. He concludes, after a survey of all the experimental evidence on the subject, that it is abundantly proved that the suprarenals are not only important but are essential to life, and that it is probable that this is due to some material yielded by the cortex—although the loss of the adrenaline which is supplied by the medulla may be contributory. Destruction of the medulla alone, the cortex having been as far as possible left intact, has not been followed by death (see also p. 101).

Various attempts have been made to produce a chronic condition of adrenal insufficiency, but it has not been possible to reproduce all the symptoms of Addison's disease experimentally, and bronzing of the skin has never been obtained in animals.³

It appears that in other diseases than Addison's, both chronic and acute, the functions of the suprarenal capsules become to a great extent suppressed (see pp. 107 and 112).⁴

¹ *Innere Sekretion*, iii. Aufl., 1916.

² *Verhndl. d. VIII. internat. zool. Kongress*, 1910.

³ For an account of such experiments, see F. A. Hartman, in Barker's *Endocrinology and Metabolism*, 1922. C. H. Kellaway and S. J. Cowell (*Journ. Physiol.*, lvii., 1923) attempted in cats to destroy the medulla by radium emanations. Beyond a certain fall of temperature they obtained no effect from the destruction, except that in two animals a shaved portion of skin appeared to show increased pigmentation. It is difficult to understand how the whole of the medulla could by this means be destroyed without the cortex being also gravely affected.

⁴ The production of symptoms accompanying suprarenal deficiency as the result of experimental operations and disease is discussed by G. N. Stewart in *Endocrinology*, v., 1921, pp. 285-306. References to the principal literature bearing on the subject will be found in this article.

CHAPTER XII

THE SUPRARENAL CAPSULES (*continued*)

FUNCTIONS OF THE CORTEX

LITTLE is positively known regarding the functions of the cortex. Its anatomical relation in mammals to the chromophil part, and the fact that its blood passes directly into the medulla, suggests that its cells may be directly concerned in the production of materials which are utilised by the medulla; but, as has been mentioned, this relation fails in many vertebrates. It has been stated¹ that the cortex contains a precursor of the adrenaline of the medulla, and that if left standing for twenty-four hours in an incubator a considerable amount of a substance giving the reactions of adrenaline accumulates within it. But it is contended that the results obtained are not ascribable to adrenaline, but to products of protein decomposition. The facts that the cortex becomes enlarged during pregnancy and is small in cases of deficient sexual development, and that changes have been described in the cortical cells accompanying the phases of the œstrous cycle, seem to afford evidence of some relationship between the functions of the cortex and the female generative glands; but whether this is direct, or operates through other ductless glands—such as the thyroid and pituitary—is not known. The occurrence of a connexion between the development of the sexual organs and that of the suprarenal cortex has been particularly insisted upon by E. E. Glynn,² who is of opinion that the cortical secretion is concerned with the differentiation and growth of the sex-cells. In young males especially numerous cases have been recorded in which sexual precocity—shown chiefly in the development of secondary sexual characters—has been associated with cortical tumours.³

The cortex increases in proportion to the growth of the body more than the medulla. It becomes augmented in size with the activity of the sexual glands in animals; also during lactation:⁴ nevertheless castration is also followed by hypertrophy. There is no clear evidence that any kind of active autacoid substance is produced by the cortical cells,⁵ and it is probable that their function

¹ Abelous, Soulié et Toujan, *C. r. soc. biol.*, lvii., 1905.

² *Quart. Journ. Med.*, v., 1912; *Journ. Obstet. and Gynæc.*, 1921.

³ See on this subject, P. G. Wooley, *Amer. Journ. Med. Sc.*, cxxv., 1903; Bulloch and Sequiera, *Trans. Path. Soc.*, lvi., 1905; H. D. Rolleston, *Goulstonian Lectures to Roy. Coll. Phys., London*, 1895; and *Montreal Med. Journ.*, Oct. 1907.

⁴ G. Verdozzi, *Policlinico*, 1915.

⁵ Voegtlin and Macht claim to have isolated a vasoconstrictor principle from chloroform extracts of the dried cortex (*Journ. Amer. Med. Assoc.*, lxi., 1913). On the other hand, Austoni got effects on the isolated mammalian heart which were antagonistic to those yielded by extracts of medulla (*Arch. ital. de biol.*, lvi., 1911).

is associated with the building up of metabolic products which are to find employment in other parts of the organism. Adler found that tadpoles fed with suprarenal cortex grew much more rapidly than controls.¹

It has been suggested that a function of the cortex may be to neutralise deleterious products which are formed in the processes of metabolism or which are introduced from outside. But this supposition has received no support as the result of experiments. It is stated, however, that oleic acid, which is present in abundance in the cortex, can neutralise tetanus toxin, and that an emulsion of cortex will antagonise snake venom.

Marine and Bannerman² found partial destruction of cortex to be followed by increased heat production and CO₂ output, a result which was prevented by removal of the thyroid.

One of the most striking facts connected with the cells of the cortex is their richness in lipoids and fats. These have been chemically investigated by many workers. In an analysis by Biedl the suprarenals of the pig yielded 74·61 per cent. of water and 25·39 per cent. of dry residue. Of the latter, 61·12 per cent. consisted of proteins, etc., and 38·88 per cent. of lipoids and fats—besides some insufficiently distinguishable extractives. In this analysis the medulla was included; as this is poor in lipoids, the lipoid contents of the cortex must have a much higher value—far higher than any other non-nervous tissue.

In some animals the lipid takes the form of doubly refracting crystals. Elliott and Tuckett³ find that the doubly refracting substance increases in amount during rest and diminishes as the result of muscular activity; this suggests a relationship between the cortex and muscular action. In the guinea-pig there are numerous brown-coloured granules in the cells—chiefly in the zona reticularis,—and Elliott and Tuckett state that these also accumulate during rest and quickly disappear with muscular work, fatty globules taking their place. Laignel-Levastine also finds that the lipoids of the cortex may almost disappear after death following extreme motor agitation.⁴

The doubly refracting lipid substances seem to consist mainly of lecithin and cholesterol—the latter in the form of esters. Rosenheim and Tebb⁵ extracted from the suprarenal cortex of the ox various fatty acids, cholesterol esters, and phosphatides, such as sphingomyelin; but not free cholesterol.

Osmic acid fixes and stains both the lipid substances and the fats: the former being stained dark grey, the latter black. After osmic fixation the blackened fat globules are insoluble in xylol, whereas the lipoids are dissolved. The birefringent substances seem to be the cholesterol ethers: they form the bulk of the lipid substances, and have been estimated by Chauffard, Laroche,

¹ *Munch. med. Woch.*, 1922.

² *Amer. Journ. Physiol.*, lvii., 1921, and lix., 1922.

³ *Journ. Physiol.*, xxxiv., 1906. Also P. Mulon, *C. r. soc. biol.*, lxxv., 1913.

⁴ *C. r. soc. biol.*, lxxxi., 1918.

⁵ *Journ. Physiol.*, xxxviii., 1909.

and Grigaut to amount to about 5.5 per cent. of the fresh substance. This would make the suprarenal cortex far richer in cholesterol than any other tissue in the body, for even nervous tissue is not found to contain more than 2.5 per cent. These authors have made a careful study of the amount of cholesterol in the suprarenals at different ages both in the foetus and after birth.¹ They have found very large differences. Thus in the third month of intrauterine life the lipid contents of the suprarenals amount to about 2.6 parts per 1000 of the fresh gland: at birth to 15 parts per 1000. There are also considerable differences in disease. The largest figures are associated with affections in which high blood-pressure is characteristic (*e.g.* cerebral hæmorrhage); but most chronic affections and febrile states exhibit a deficiency: this is perhaps best marked in pulmonary tuberculosis. Corresponding with the excess or deficit of cholesterol in the suprarenals there is an increase or diminution of the same substance in the blood, a fact which appears to support the opinion that the cortex not only serves as a storehouse for these lipid substances, but that it is a factory for them. It is not a little remarkable to find that in diseases associated with hypertension of blood (see Table, p. 108), in which it might certainly be expected from the symptoms that an excess of adrenaline is produced by the suprarenal medulla and passed into the blood there is an increase of cholesterol in the suprarenal cortex and in the blood. It must, however, be added that excess of cholesterol in the blood is not always associated with hypertrophy of the suprarenal cortex, for an excess is found in the blood in certain affections of the liver, without hypertrophy or even with diminution of the cortex.

Various experiments have been made to determine whether the suprarenal cortex does actually form and secrete lipoids into the blood. Troisier and Grigaut,² after removal of one suprarenal in the dog, found that for the first three or four days the percentage of cholesterol in the blood remained normal, but that it then rose so that in a short time it was double or treble the normal amount: they ascribe this to a superactivity of the cortex of the remaining gland, which is stated to show signs of enhanced cell-activity and to contain an increased amount of lipoids.³ Porak and Quinquaud⁴ found that saponine, which does not affect the secretion of adrenaline into the blood, augments that of cholesterol. It is stated by the same authors that stimulation of the splanchnics, which causes an outpouring of adrenaline into the blood, has no effect upon the cholesterol content of the blood of the suprarenal veins.

Considering the wide distribution of lipoids, and especially of cholesterol, in the organism, and that they form an important part of the chemical structure of protoplasm and are probably essential to its functions, if it should be the case that the main function of the suprarenal cortex is the manufacture of these substances, one can understand why their removal by operation or their destruction by disease should be incompatible with the prolonged maintenance of life.⁵

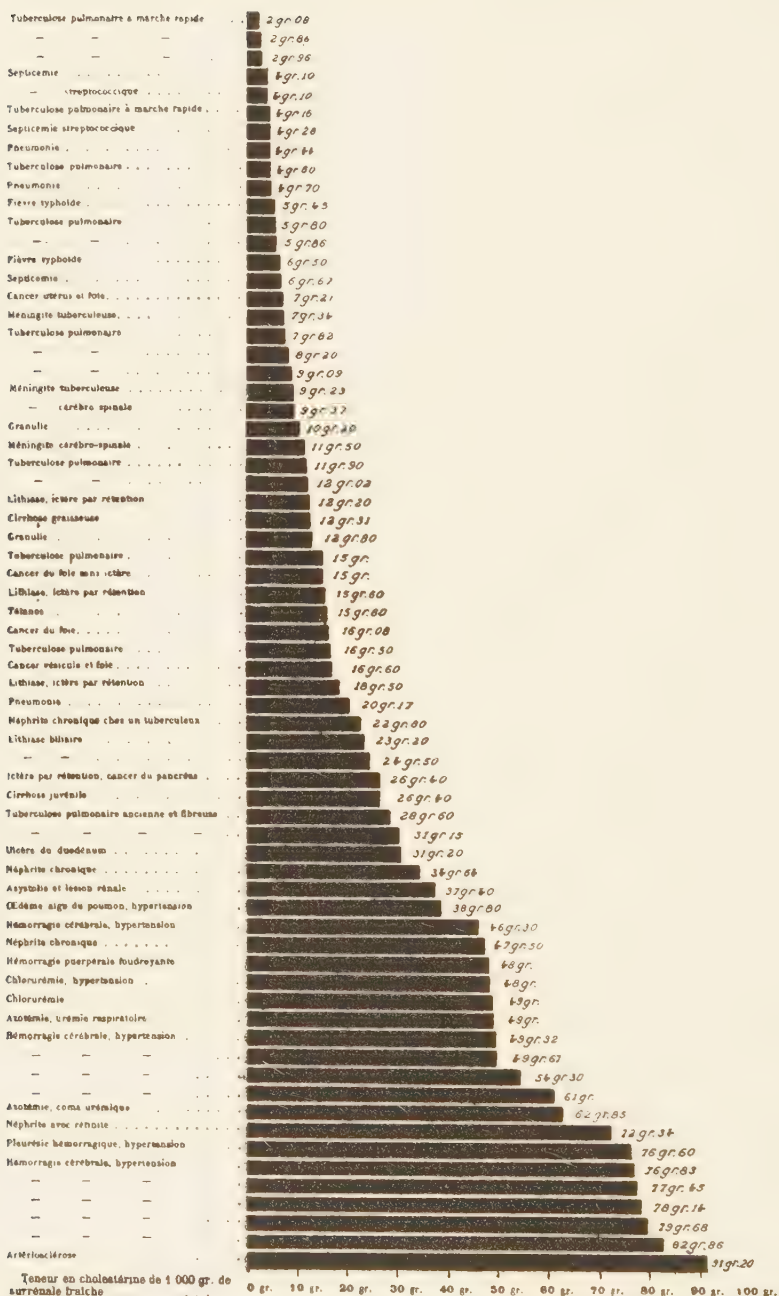
¹ *C. r. soc. biol.*, lxxxi., 1918.

² *Presse méd.*, 1912.

³ Complete decapsulation is not followed by an increase of cholesterol in the blood (Baumann and Holly, *Journ. Biol. Chem.*, lv., 1923).

⁴ *C. r. soc. biol.*, lxxvii., 1914.

⁵ Clevers and Goormatigh (*Bull. acad. roy. méd. Belg.*, 1922) find that diphtheria toxin causes an increase of cholesterol in the suprarenal cortex.



The accompanying table from Chauffard, Laroche, and Grigaut¹ serves to illustrate the great variations which occur in the relative amount of cholesterol in the suprarenals after death from various diseases.²

The suggestion that the suprarenal cortex may be a seat of manufacture of lipoids of the body, and may especially be related to the formation and development of the myelin of nerve-fibres, is attractive. And the fact that in the human foetus and infant so large a development of suprarenal cortex occurs—which is missed in the anencephalous monster—seems to indicate a connexion between the development of the substances formed in the cortex and those constituting the cerebral hemispheres. But against this idea we have the observation of Elliott and Armour³ that the superadded part of the suprarenal cortex in the foetus does not contain the doubly refracting lipid substances which are characteristic of the ordinary cortical cells. Nor does the doubly refracting lipid matter occur in all animals: in many species it is absent. This is the case with all adult ruminants examined, although it occurs in some in the young state. During pregnancy lipoids are said to increase in amount not only in the suprarenals but in all organs of the body.

It is stated that feeding with cholesterol (rabbits) causes hypertrophy of the suprarenal cortex and an increase in amount of its lipoids.⁴

An important substance contained in the cortex is *choline*,⁵ which enters into the composition of the phosphatides. This, when free, lowers blood-pressure by affecting the vagus-endings in the heart, producing inhibition and diminution of force. It causes excitation of the intestinal movements, whereas the usual effect of adrenaline is to inhibit them. It also antagonises the effect of adrenaline in producing glycæmia and glycosuria. Choline is, however, not specific to the suprarenal capsules but occurs to a variable extent in most tissues and organs.⁶

G. M. Findlay⁷ finds that the lipochrome in the suprarenals can be varied by altering the lipochrome content of the food. It is increased in acute infectious diseases and still more in chronic affections, in which there is almost always a deposition of melanin in the cells, both cortical and medullary.

¹ *Congrès français de méd.*, 1920 (reproduced from the French edition of this book).

² Numerous papers on this subject have appeared in *C. r. soc. biol.*, from 1902 to 1920, by L. Bernard and Brigart, P. Mulon, and Chauffard, Laroche, Guy, and Grigaut. It is also treated at some length by Laroche and Richard in the French translation of this work. The content of the cortex in lipoids in various nervous and mental diseases is dealt with by Vasilescu in *Bull. et mém. soc. de neurol., etc., de Jassy*, iii., 1922.

³ *Journ. Path. and Bact.*, xv., 1911.

⁴ D. D. Krylow, *Ziegler's Beitr.*, lviii., 434 and 469, 1914.

⁵ A. Lohmann, *Arch. f. d. ges. Physiol.*, cxviii., 1907.

⁶ See on the chemistry of choline, G. Barger, *The Simpler Natural Bases*, 1914.

⁷ *Journ. Path. and Bact.*, xxiii., 1920.

CHAPTER XIII

THE SUPRARENAL CAPSULES (*continued*)

THE NATURE OF THE AUTACOID FURNISHED BY THE MEDULLA : ADRENALINE

ALL the physiological effects which are about to be described as yielded by suprarenal extracts are obtainable from extract of medulla alone : intravenous injection of extract of cortex gives no appreciable result.¹ In elasmobranch fishes, in which the cortex is represented by the interrenal body and the medulla by the entirely separate "paired bodies" of Balfour (fig. 52), it was shown by Vincent that the latter yield an active extract, whilst extracts of the interrenal body are inactive.²

The action of the extract of medulla is due to the material within the cells which becomes stained brownish yellow with chromic salts, and which, as Vulpian³ had shown, gives characteristic colour reactions with various agents : similar reactions were obtained by Vulpian with the blood of the suprarenal vein.

B. Moore⁴ showed that the blood-pressure raising property is in direct proportion to the intensity of Vulpian's material, which became known as chromogen, chromaffin, or chromaphil substance.

This "chromaphil substance" of the suprarenal medulla, after being partly isolated by S. Fraenkel,⁵ was prepared in a condition approaching purity by v. Fürth⁶ and by Abel,⁷ and obtained eventually in a crystalline form by Takamine⁸ and by Aldrich.⁹ It received various names, such as *suprarenin* (v. Fürth), *epinephrin* (Abel), *adrenalin* (Takamine), the last being that by which it has been most widely known. This name has been adopted in the British Pharmacopœia and will therefore be employed in this work, but with the addition of the final *e* (*adrenaline*) to denote its amine nature.¹⁰

¹ Oliver and Schafer, *Journ. Physiol.*, xvi., 1894 ; xvii., 1895 (*Proc. Physiol. Soc.*), and xviii., 1895. (See, however, note 5 on p. 105).

² *Proc. Roy. Soc.*, lxi., 1897.

³ *C. r. acad. sci.*, xliii., 1856.

⁴ *Journ. Physiol.*, xvii., 1895, and xxi., 1897.

⁵ *Wien. med. Bl.*, xix., 1896.

⁶ *Zeitschr. f. physiol. Chem.*, xxiv., 1897 ; xxvi., 1898 ; xxix., 1900.

⁷ *Ibid.*, xxviii., 1899 ; *Amer. Journ. Physiol.*, iii., 1900, and viii., 1902 ; *Johns Hopkins Hosp. Bull.*, xii., 1901, and xiii., 1902.

⁸ *Amer. Journ. Pharm.*, lxxiii., 1901.

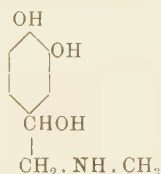
⁹ *Amer. Journ. Physiol.*, v., 1901, and vii., 1902. Aldrich gave the formula for adrenaline as $C_9H_{13}NO_3$, and this has usually been accepted as correct.

¹⁰ The history and chemistry of adrenaline is very fully dealt with by Barger in his book *The Simpler Natural Bases*, to which the reader is referred for details which cannot be introduced here. A good short account is given by T. Stephenson in the *Prescriber*, xvii., 1923.

It has been estimated that the suprarenal capsules contain about 1 part of adrenaline per 1000 of the whole gland, but as it only occurs in the medulla, which forms less than a fourth of the gland, the proportion in this would be by so much greater.¹ Since each suprarenal weighs about 5 grams, the amount of adrenaline in the two would be about 10 mgr.

Adrenaline can be prepared synthetically from catechol; methyl-amino-aceto-catechol² being first obtained. This when reduced gives a racemic salt which can be separated by methyl alcohol into *d*-adrenaline and *l*-adrenaline.³ The latter appears to be in all respects identical with the natural product, while the racemic salt and *d*-adrenaline are much less active physiologically.⁴

Chemically adrenaline is lævo-methylamine-ethanol-catechol.⁵



The chemical tests for adrenaline depend upon the colour yielded by certain reagents. Thus ferric chloride produces a bright green colour, changing to violet and red on addition of alkali. Iodine solutions and most oxidising reagents give a rose colour, which also appears in solutions of adrenaline on exposure to air. Mercuric chloride in presence of sodium acetate also gives a rose-red colour: it is stated that 1 part in 40,000 can be detected by this. Folin's reagent—a solution of sodium tungstate (100 g.) in water (750 c.c.) with 80 c.c. of an 85 per cent. phosphoric acid solution added—gives a blue colour, and is said to be able to detect adrenaline in a dilution of 1 in 3 millions; it is also used for quantitative determinations.⁶

The amount of adrenaline is normally about the same in each suprarenal.⁷ There is less in infants and much less in the foetus, where Moore and Purinton,⁸

¹ Batelli, *C. r. soc. biol.*, 1902; T. R. Elliott, *Journ. Physiol.*, xliv., 1912. A. Richard gets a higher percentage (*C. r. soc. biol.*, lxxxvi., 1922).

² Sometimes termed "adrenalone." This substance has similar physiological effects, but is much less active than adrenaline.

³ Flücher, *Zeitschr. f. physiol. Chem.*, lviii., 1908.

⁴ A. R. Cushny, *Journ. Physiol.*, xxxvii., xxxviii., 1908; W. H. Schultz, *Bull. Hyg. Lab. Washington*, No. 55, 1909, and *Journ. Pharm. and exp. Ther.*, i., 1909; Fröhlich, *Zentr. f. Physiol.*, xxiii., 1909, and xxv., 1911; Abderhalden (and others), *Zeitschr. f. physiol. Chem.*, lviii., lix., lxi., and lxii., 1908 and 1909.

⁵ Pauly, *Ber. d. chem. Ges.*, xxxvi., 2944, 1904; Friedmann, *Beitr. z. chem. Physiol.*, vi., 1904, viii., 1906.

⁶ Folin, Cannon, and Denis, *Journ. Biol. Chem.*, xiii., 1913. See also Barger, *op. cit.* For a modification by Kodama, see *Chem. Soc. Abstr.*, Feb. 1923. A still more delicate test has been described by Russmann (*Klin. Wochenschr.*, i., 1922).

⁷ T. R. Elliott, *Journ. Physiol.*, xliv., 1912; Stewart and Rogoff, *Journ. Exper. Med.*, xxiv., 1916. After removal of one gland the amount in the other is much increased.

⁸ *Amer. Journ. Physiol.*, iv., 1900.

Elliott¹ and J. H. Lewis² failed to find it except in small amount, although Elliott found a large quantity in the aortic paraganglion of the foetus (see fig. 54). C. P. M'Cord was able to detect it in the capsules as early as the sixth week³ and Cevolotto in the middle of pregnancy.⁴

Prolonged administration of chloroform causes adrenaline to diminish, and eventually to disappear from the medulla of the suprarenals.⁵

The content of the suprarenals in adrenaline is materially affected by disease.⁶ For the effects of deprivation of vitamins, and of inanition, see p. 93.⁷

¹ *Journ. Physiol.*, xlv., 1913 (*Proc. Physiol. Soc.*).

² *Journ. Biol. Chem.*, xxiii., 1915.

³ *Journ. Biol. Chem.*, xxiii., 1915. Svehla did not find it in the human embryo, but was able to detect it very early in the ox embryo (*Arch. f. exper. Path. u. Pharm.*, xliii., 1900), and Fenger in ox, pig, and sheep embryos a few weeks after conception (*Journ. Brit. Chem.*, 1912).

⁴ *Atti r. istit. Veneto*, 1916.

⁵ Delbet, Herrenschildt, and Beauvy, *Presse méd.*, March 6, 1912. See on the effects of anæsthetics, J. F. Corbett, *Journ. Amer. Med. Assoc.*, lxxix., 1922.

⁶ For the amount in various diseases, see S. Ohno, *Verhandl. d. jap. path. Ges.*, 1916; F. Lucksch, *Virch. Arch.*, cxxiii., 1917; and E. Bauer, *ibid.*, ccxxv., 1918. The effect of diphtheria toxin in reducing the amount of adrenaline in the suprarenal capsules has been noted by various observers (Elliott and Tuckett, *op. cit.*; Lucksch, *Verhandl. d. Deutsch. path. Gesell.*, 1910; J. Ritchie and Ninian Bruce (*Quart. Journ. Exper. Physiol.*, iv., 1911). The toxin of cholera has the same effect (Déméstreescu, *C. r. soc. biol.*, lxxvii., 1914). Newburgh and Kelly (*Arch. intern. Med.*, x., 1912) were unable to show any diminution of adrenaline in the suprarenals after injection of tubercle toxin, but in fevers and most exhausting diseases it is greatly diminished or absent. (Sydenstricker, Delatour, and Whipple, *Journ. Exper. Med.*, xix., 1914, "The Adrenaline Index of the Suprarenal Glands in Health and Disease").

⁷ For statistics regarding the amount of adrenaline in the suprarenals under various conditions see F. Batelli, *C. r. soc. biol.*, liv., 1902.

CHAPTER XIV

THE SUPRARENAL CAPSULES (*continued*)

EFFECTS OF EXTRACT OF THE MEDULLA (OR OF ADRENALINE) ON THE CIRCULATORY AND RESPIRATORY SYSTEMS

IF a water or saline extract or decoction of the medulla is injected into a blood-vessel, an immediate and marked rise of blood-pressure is produced.¹ This is caused by contraction of the peripheral arteries. The effect of the contraction is to produce shrinkage of any organ or part the arteries of which are especially affected: such shrinkage may be recorded by a plethysmograph (figs. 65, 69, 71). Along with the vascular contraction a slowing of the heart's action (or even complete stoppage of auricular beats) may occur, due to an effect on the cardio-inhibitory centre, and this may somewhat limit the rise of blood-pressure (fig. 60). But if the vagi are cut, or paralysed by atropine, the heart-beats become greatly accelerated and augmented in force (primarily by the action of the autacoid on the auricles, but also somewhat on the ventricles),² and this greatly increases the rise of blood-pressure (fig. 61). If the amount injected is considerable, the rise of blood-pressure caused by vascular contraction and heart acceleration may be enormous—three or four times the normal—and the amount of strain put on the heart is correspondingly great. Sometimes the heart muscle is unable to contract rhythmically and regularly under these circumstances, and the ventricular action becomes “fibrillar”—*delirium cordis* being produced, generally leading to instant death (fig. 62). This seems especially liable to occur in a particular phase of early chloroform anaesthesia.³

According to MacWilliam,⁴ ventricular fibrillation is more liable to be produced by comparatively small doses of adrenaline than by larger doses, which may even abolish it if established. J. A. Gunn, however, states that strong solutions are more liable to produce fibrillation than weak ones,⁵ and this is my own experience. The mode of production of the fibrillation is not clear, but such fibrillation is liable to be caused by any intense stimulation of cardiac muscle, or by

¹ Oliver and Schafer, *Journ. Physiol.*, *op. cit.*, 1894 and 1895: N. Cybulski and Symonowicz, *Anz. d. Krak. Akad.*, 1895.

² It has been shown in cases of complete heart-block—experimental and clinical—that administration of adrenaline causes acceleration of ventricle as well as auricle, although they are contracting independently (Hardoy and Houssay, *Arch. de physiol.*, xvii., 1918).

³ A. G. Levy, *Proc. Physiol. Soc.*, *Journ. Physiol.*, xlii., 1911.

⁴ *Proc. Roy. Soc.*, B, xc., 1918.

⁵ *Quart. Journ. Exper. Physiol.*, vii., 1914.

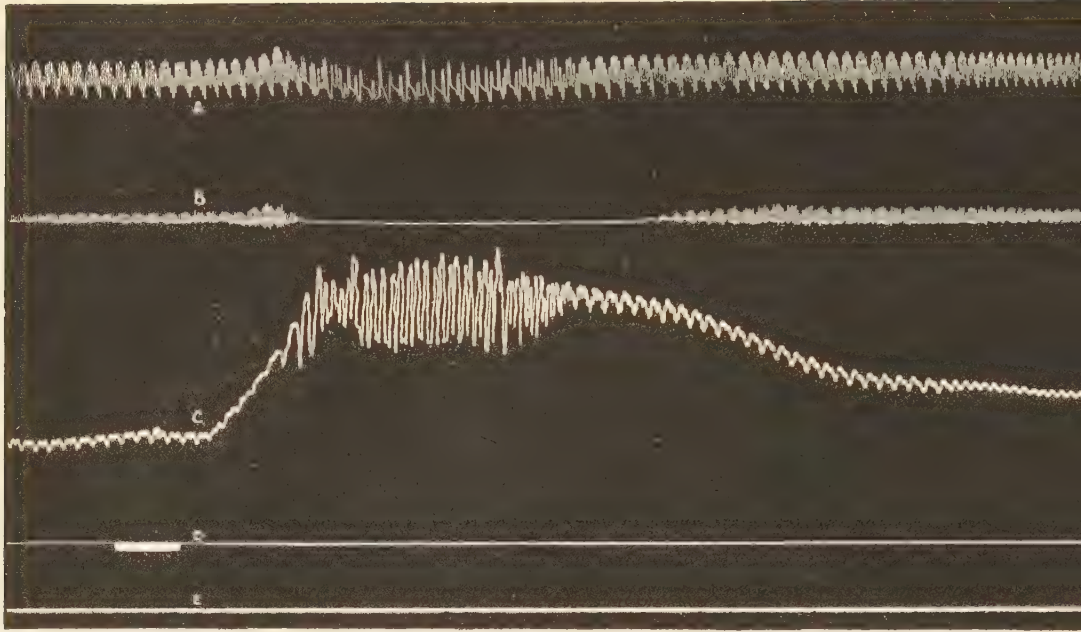


FIG. 60.—Effect upon heart and blood-pressure of injecting suprarenal extract into a vein, with vagi intact (dog). (This figure, as well as figs. 61, 62, 63, 65, and 71, are from Oliver and Schafer, *Journ. Physiol.*, 1895, vol. xviii.)

A, ventricle; B, auricle; C, arterial pressure; D, signal; E, time-marking in seconds. The tracings in these figures have been reduced to rather less than half the size of the originals.

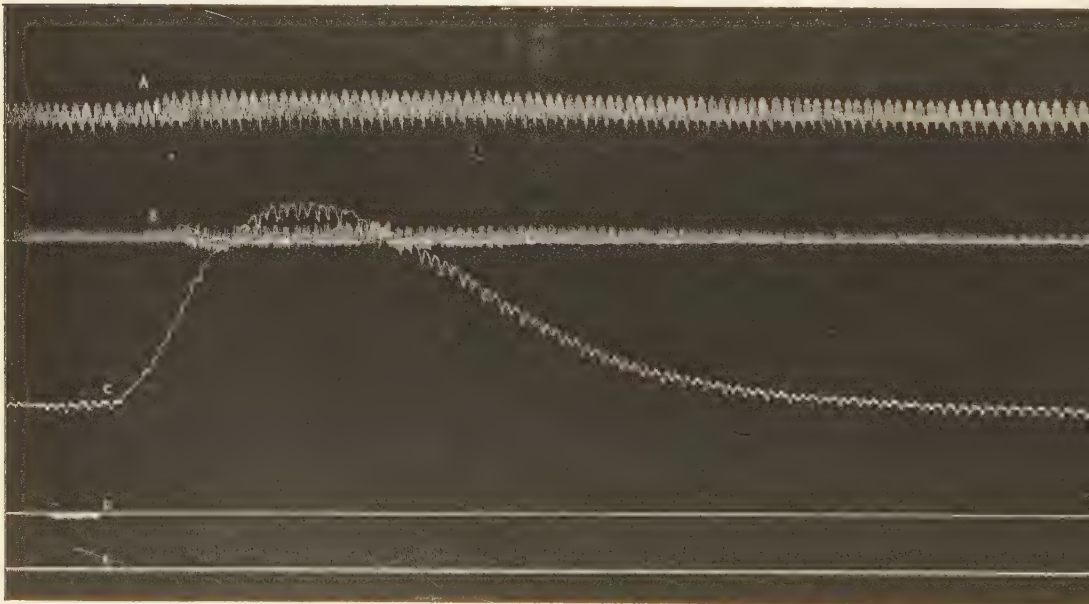


FIG. 61.—The same as fig. 60, but with vagi cut.

interference with the flow of blood in the coronary vessels.¹ I have seen it abolished in cats by double vagotomy, but it is generally too rapidly fatal for any effective measures to be taken to overcome it.² The most helpful treatment is intermittent digital pressure on the ventricles so as to maintain some sort of circulation until the heart can recover.

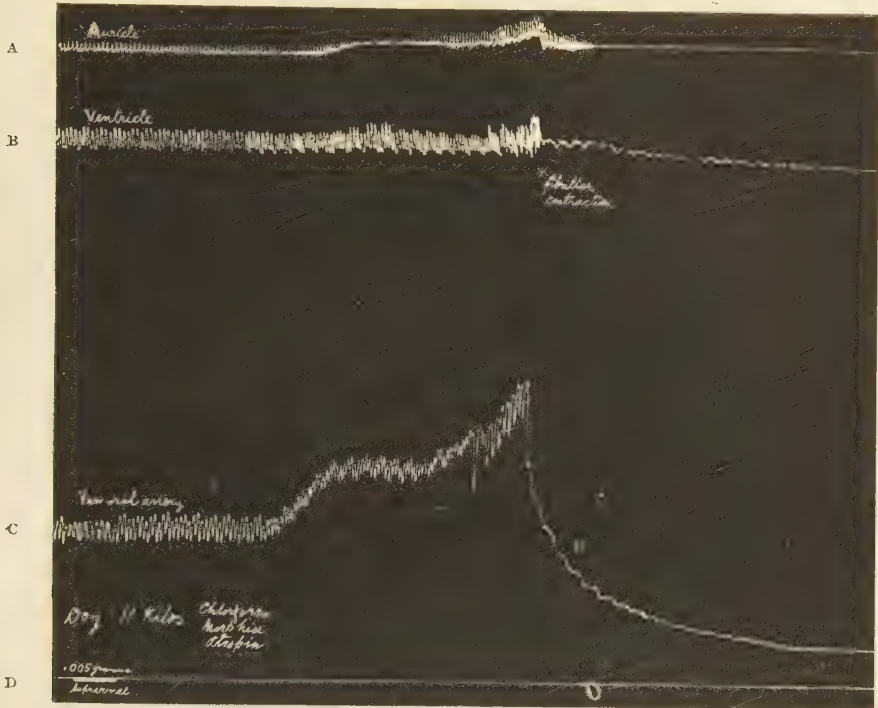


FIG. 62.—Fibrillation of ventricle of dog produced by intravenous injection of extract of ox suprarenal: 0.01 g. of the whole gland.

A, auricle; B, ventricle; C, blood-pressure (femoral); D, signal and zero of blood-pressure. The waves, which are seen after the heart has passed into fibrillation, are respiratory. (Notice that the ventricle has ceased to act before the auricle.)

As was noted by Oliver and Schafer, there is some diminution in the depth of the respirations (fig. 63), and occasionally a temporary cessation of breathing (adrenaline apnoea, fig. 64). But this disappears long before the effect on the blood-vessels has ceased to show itself.

It was ascribed by us to contraction of blood-vessels in the medulla oblongata,³ but J. Bouckaert⁴ states that it occurs in the cat even after ergotoxine,

¹ See on the causes of ventricular fibrillation, J. MacWilliam, in *Brit. Med. Journ.*, Aug. 11 and 18, 1923.

² In the case illustrated by fig. 62, the action of the vagi had been abolished by atropine.

³ See also F. Roberts, *Journ. Physiol.*, lv., 1921, and lvi., 1922, who finds that a Cheyne-Stokes respiration is sometimes caused by adrenaline.

⁴ *Arch. néerl. de physiol.*, vii., 1922.

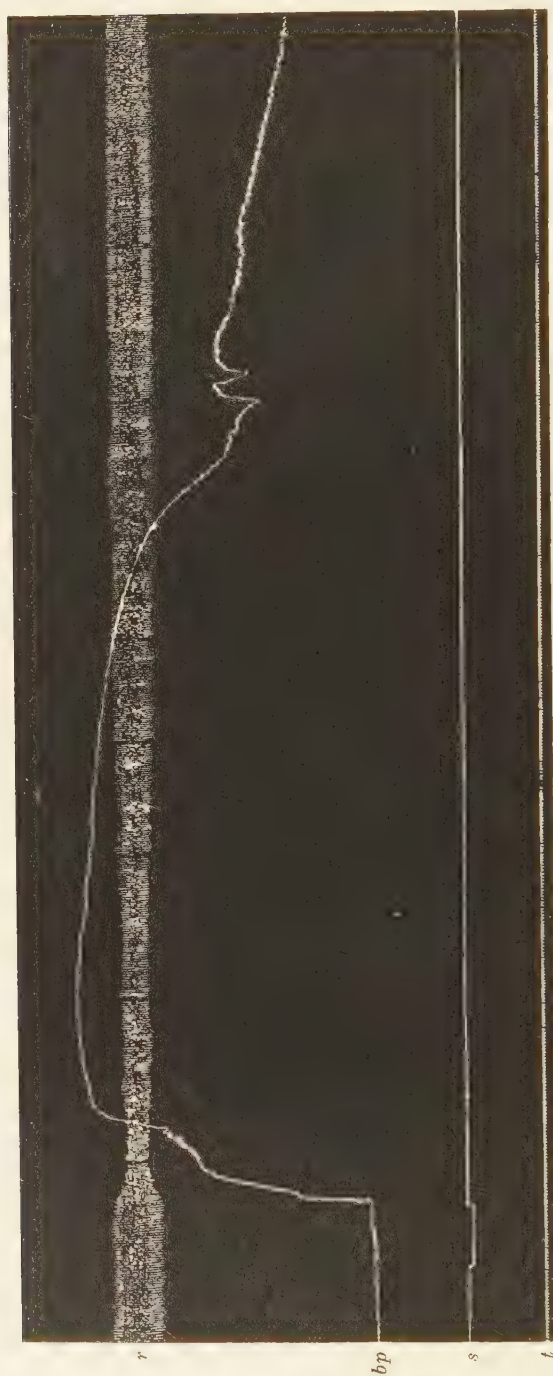


FIG. 63.—Effect of extract of suprarenal upon the blood-pressure and respiratory movements of rabbit.

r., respirations ; bp., blood-pressure ; s., signal and line of ϕ -pressure ; t., time in secs.

which converts the constrictor action of adrenaline into a dilating action, and concludes that the autacoid has therefore a direct chalone or paralysing action on the respiratory centre. J. Mellanby and Huggett¹ state, however, that adrenaline apnoea is prevented by ergotoxine; while, on the other hand, vagal apnoea is not affected by that drug. Langlois and Garrelon found that in the dog either diminution or increase of respirations might occur as the result of administration of adrenaline, the effect depending upon the condition of the

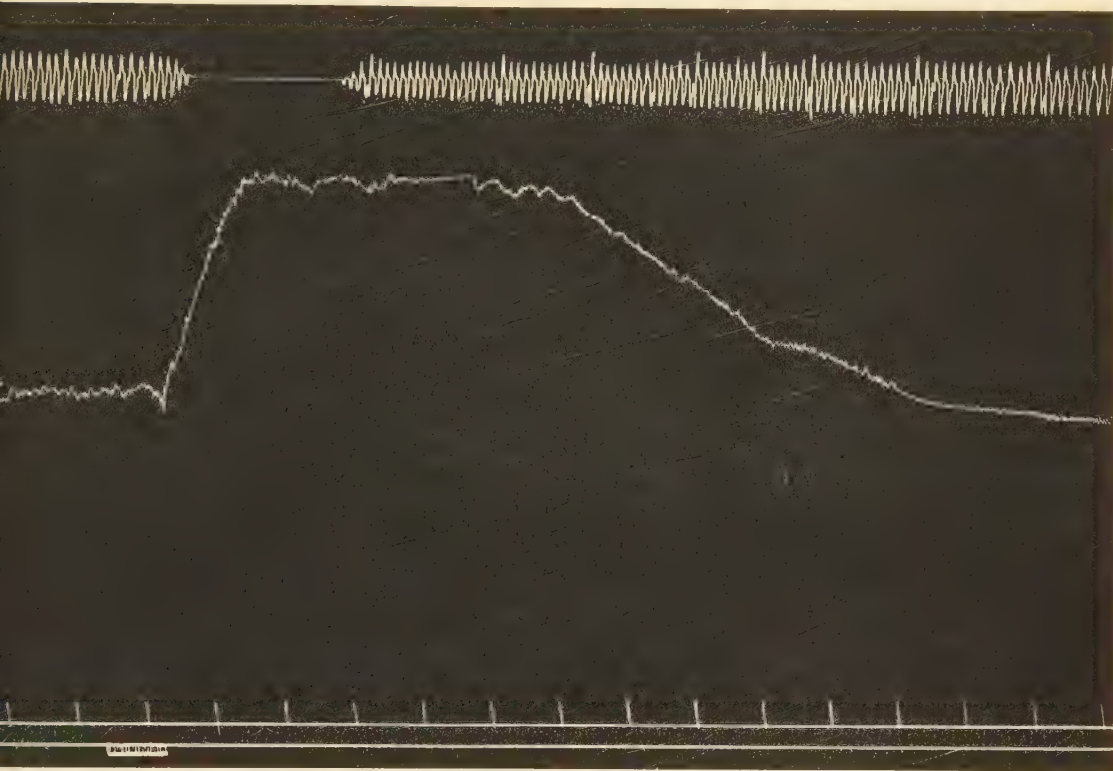


FIG. 64.—Adrenaline apnoea in cat.

r., respirations (the upstroke indicating inspiration); *bp.*, blood-pressure; *t.*, time in 10 secs.; *s.*, signal.
(Reduced to $\frac{1}{10}$.)

respiratory centre at the time.² But, according to Nice, Rock, and Courtwright, the effect depends on the dose, small doses stimulating and large doses inhibiting the respiratory centre.³

The effect upon the vessels lasts a few minutes, gradually passing off; after its passage the blood-pressure is usually a little lower than before.

¹ *Journ. Physiol.*, lvii., 1923.

² *Journ. de physiol.*, xiv., 1912.

³ *Amer. Journ. Physiol.*, xxxiv., 1914.

After the immediate action of the autacoid has passed off the presence of adrenaline in the blood of animals which have received even a considerable intravenous injection cannot be shown even by the most delicate methods. It must therefore be very rapidly destroyed, or otherwise rendered inactive in the body. This subject will be referred to later.

With very minute doses of adrenaline (1 to 3 mgr. per kilog. body weight) a fall of blood-pressure may be obtained instead of a rise.¹ Even with larger doses the usual rise is sometimes preceded by a fall. This seems to be due to the fact that at the beginning of an injection the dose of adrenaline is more diluted, and a very dilute solution produces dilatation of arteries instead of contraction; at any rate in carnivora. F. A. Hartman² found that a dose of 0.2 c.c. of a 1 in 100,000 solution almost always causes dilatation of the vessels of the limbs, although there may be contraction of the vessels of the splanchnic area. But if such a dose is given after a considerable hæmorrhage, a general contraction of vessels is produced.

The vaso-inhibitory effect of small doses is readily seen in the cat,³ but it is absent in the young kitten,⁴ appearing at about 11 weeks for the limb vessels and rather later for the mesenteric vessels. In the dog large doses of the autacoid produce flushing of the lips and buccal mucosa⁵ but pallor of the tongue: effects which are obtained by stimulating the cervical sympathetic (Dastre).

If it requires a smaller dose of adrenaline to cause dilatation of the blood-vessels than to cause constriction, dilatation rather than constriction must be regarded as the primary effect of the autacoid on the blood-vessels. According to Hartman and Fraser,⁶ the vaso-dilatation caused by a minute dose of adrenaline fails if the nerves to the vessels have been cut, but if these are left intact and the limb or other organ is separately perfused, the injection of adrenaline in small amount into the blood circulating in the body of the animal causes the limb or other isolated organ to swell. Destruction of the brain does not affect the result, nor destruction of the cord. The mechanism must therefore be in the sympathetic or spinal ganglia. Destruction of the sympathetic ganglia or painting them with nicotine abolishes the effect on the intestine: destruction of the spinal ganglia abolishes the effect on the hind limb.

Action on Different Vessels.—Adrenaline does not act equally or in the same manner on all vessels. With moderate doses those of muscle are dilated by it,

¹ Moore and Purinton, *Arch. f. d. ges. Physiol.*, lxxxi., 1900. G. A. Pari, *Arch. ital. de biol.*, xlv., 1905.

² *Amer. Journ. Physiol.*, xxxviii., 1915.

³ Cannon and Lyman, *Amer. Journ. Physiol.*, xxxi., 1913. They regard it not as the effect of stimulation of inhibitory fibres, but as dependent upon the condition of the tone of the vessels at the time.

⁴ Hartman and Kilborn, *Amer. Journ. Physiol.*, xlv., 1918. For fuller observations on the dilator effects of adrenaline in the cat and dog, see Hartman, Kilborn, and Fraser, *ibid.*, xlv., 1918; and Wertheimer, *Arch. néerl. de physiol.*, vii., 1922. For the pressor and depressor effects produced by adrenaline and the effects of tissue extracts on the reactions, see J. B. Collip, *Amer. Journ. Physiol.*, liii., 1920, and *Endocrinology*, vi., 1922; also R. G. Hoskins, *Physiol. Revs.*, ii., 1922.

⁵ E. Wertheimer, *Arch. néerl. Physiol.*, vii., 1922.

⁶ *Amer. Journ. Physiol.*, xlv., 1920.

while those of the skin are contracted. Hence the limbs are sometimes expanded (fig. 71), sometimes contracted (fig. 65); after removal of the skin they always expand. The intestinal vessels are usually strongly contracted, but may be dilated even by large doses, although the dilatation is preceded by contraction.¹ Ergotoxine causes paralysis of the vaso-constrictors, and after administration of this drug adrenaline always produces dilatation.²

That the direct application of extract of suprarenal medulla (*i.e.* of adrenaline) to the smaller blood-vessels causes intense local constriction, was shown by G. Oliver.³ A solution of this autacoid, in fact, furnishes the surgeon with one of his most valuable styptics.

It was shown by MacWilliam⁴ that adrenaline causes a ring cut from a large artery to contract. This effect can be produced long after general death.

The effect of injection of adrenaline solution subcutaneously into the ear of the rabbit produces a greater and much more prolonged local effect upon the vessels of the ear than its introduction intravenously,⁵ and a much greater effect than stimulating the cervical sympathetic.

The arteries of the brain are usually only very slightly affected. Dixon and Halliburton⁶ obtained dilatation on adding adrenaline (1 per 1000 solution) to Ringer's fluid used to perfuse a dog's brain. Wiggers,⁷ however, obtained contraction in most of his perfusion experiments, and Biedl and Reiner⁸ have shown that the cerebral arteries contract on direct application of adrenaline. Cow,⁹ however, obtained relaxation of arterial rings (in confirmation of Gerhardt),¹⁰ and probably, as with many other organs, adrenaline produces both effects under different conditions.

The arteries of the coronary circulation are often said to be unaffected; although it is difficult to determine this point in the intact heart, since the extreme acceleration and augmentation of its action causes mechanically an increased flow through the coronary vessels, which might therefore be thought to be dilated.¹¹

¹ See F. A. Hartman, *Amer. Journ. Physiol.*, xxxviii., 1915; Hoskins, Gunning, and Berry, *ibid.*, xli., 1916; R. G. Hoskins, *Endocrinology*, i., 1917; Hartman and Fraser, *Amer. Journ. Physiol.*, xlv., 1917.

² H. H. Dale, *Journ. Physiol.*, xxxiv., 1906.

³ *Proc. Physiol. Soc., Journ. Physiol.*, xvii., 1895.

⁴ *Proc. Roy. Soc.*, lxx., 1901. See also O. B. Meyer, *Zeitsch. f. Biol.*, xlviii., 1906; and F. Müller, *Arch. f. Physiol.*, Suppl., 1906.

⁵ Auer and Meltzer, *Journ. Pharm. and Exper. Therap.*, ix., 1917. The experiment succeeds also with the surviving vessels in the freshly killed animal (del Campo, *Zeitschr. f. Biol.*, lxix., 1918).

⁶ *Quart. Journ. Exper. Physiol.*, iii., 1910.

⁷ *Amer. Journ. Physiol.*, xiv., 1905, and xlviii., 1914.

⁸ *Arch. f. d. ges. Physiol.*, lxxiii., 1898, and lxxix., 1899.

⁹ *Journ. Physiol.*, xlii., 1911.

¹⁰ *Arch. exper. Path. u. Pharm.*, xlv., 1900.

¹¹ Schafer, *Arch. d. sci. biol.*, St Pétersbourg, 1904; T. R. Elliott, *Journ. Physiol.*, xxxii., 1905. Brodie and Cullis got both contraction and dilatation, the latter with large doses (rabbit), *Journ. Physiol.*, xliii., 1911.

Wiggers¹ always obtained constriction of coronaries, but according to Barbour and Prince² the coronary arteries of man and monkey are contracted by adrenaline, whilst those of other animals are dilated. The determination of the action, if any, is usually made either by perfusing the vessels or by immersing rings of artery in Ringer's solution to which adrenaline is added (MacWilliam's method). Argyll Campbell³ obtained (in sheep, dog, and cat) either slight contraction of perfused coronary vessels from adrenaline or no effect, but isolated portions of coronary artery (ox, sheep) were generally relaxed by the autacoid. This had previously been found by Langendorff⁴ and by Pal.⁵

Rothlin⁶ found that isolated rings of coronary artery of the ox contract in very dilute solutions of adrenaline, but relax in stronger solutions, whilst with similar rings from the horse he almost always obtained relaxation with all strengths.

It is the smaller arteries which are most affected by adrenaline. In consequence of the great rise of pressure which their contraction produces, the larger arteries may become passively dilated: this dilatation may even be very great. The constricting effect on the arteries is seen after complete destruction of the central nervous system, and also after severance of the nerves to the part (fig. 65). It is therefore due to a direct action upon the peripheral vessels.

This is contrary to the conclusion arrived at by Cybulsky and Symonowicz (*op. cit.*), who supposed that the action was upon the vasomotor centre in the medulla oblongata. It is possible that there may be some slight stimulation of that centre with large doses, but if so it is probably an indirect effect of the anæmia caused in the medulla by contraction of its arteries.⁷

Repeated intravenous injections into the ear-vein given at intervals of a few days produce (in the rabbit) degenerative sclerosis of arteries.⁸ This action is not specific to the suprarenal autacoid, but may result from prolonged abnormally high blood-pressure, however produced.⁹

The effect of adrenaline on venous blood-pressure varies considerably, and is largely dependent upon its effect on the arteries and perhaps also on the capillaries. But H. Connett¹⁰ has shown that a ring cut from a large vein will contract with adrenaline like a similar ring from an artery. Previously, however, J. A. Gunn and Chavasse¹¹ found that adrenaline acts upon the

¹ *Amer. Journ. Physiol.*, xxiv., 1909.

² *Journ. Exper. Med.*, xxi., 1915.

³ *Quart. Journ. Exper. Physiol.*, iv., 1911. See also on this subject, E. A. Park, *Journ. Exper. Med.*, xvi., 1912.

⁴ *Zentrbl. f. Physiol.*, xxi., 1907.

⁵ *Wien. med. Woch.*, 1909.

⁶ *Wien. tierärzt. Monatschr.*, 1921. For other observations, see Tigerstedt, *Physiol. d. Kreislaufes.*, Bd. iv., p. 78, 1923.

⁷ Lagus and Kunas, *Skand. Arch. f. Physiol.*, lxiii., 1917. Cardiac inhibition such as is shown in fig. 60 is probably brought about in the same way (Oliver and Schafer, *op. cit.*).

⁸ O. Josué, *C. r. soc. biol.*, lv., 1903; M. Loeper, *ibid.*

⁹ Batty Shaw, however, got the degeneration even when he injected amyl nitrite at the same time in sufficient amount to neutralise the pressor effect of adrenaline, and concludes that it is a toxic effect, and not due to high blood-pressure (*Brit. Med. Journ.*, 1910).

¹⁰ *Amer. Journ. Physiol.*, liv., 1920.

¹¹ *Proc. Roy. Soc.*, B, lxxxvi., 1912-13.

muscular coat of veins, causing tonic contraction. They noticed that it produces increased rhythmic contraction of the superior vena cava near the heart. The portal vein and its branches also contract, causing a diminution in the blood-flow to the liver and a considerable rise in the blood-pressure in the vein.¹ Probably it also causes the hepatic veins to contract, since, as Starling has shown, it increases the amount of lymph flowing from the liver.

Adrenaline also appears to act upon the capillaries, producing contraction,² probably of the cells of Rouget in their wall. This is not, however, a constant effect.

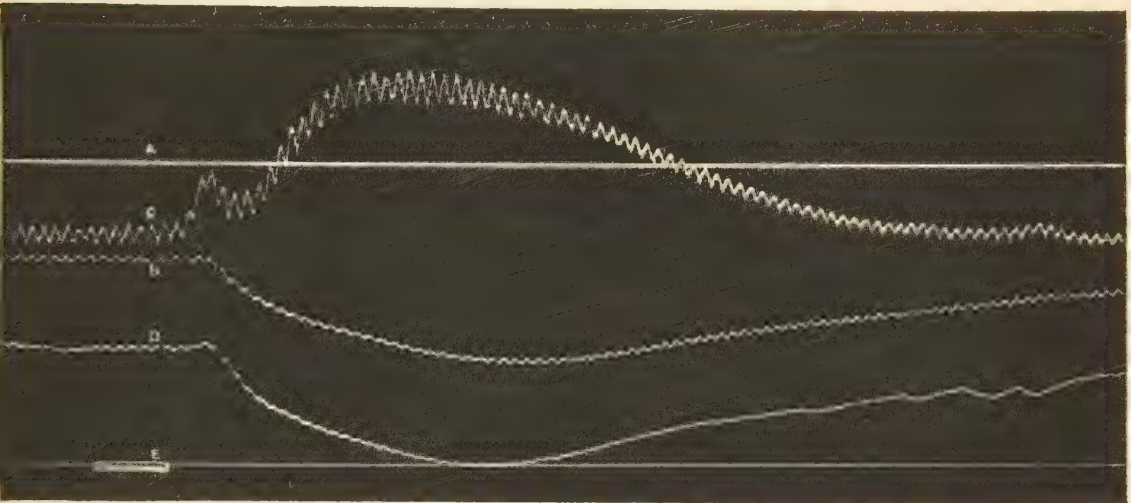


FIG. 65.—Effect upon blood-pressure and limb volume of injecting suprarenal extract into a vein (dog).

A, time-marking (seconds); C, arterial pressure; B, volume changes of left fore limb, nerves intact; D, volume changes of right fore limb, brachial plexus cut (notice the large waves on the rising curve); E, signal; the line records abscissa of blood-pressure.

The dilatation of the limbs is mainly due to the vessels of the muscles:³ those of the skin are contracted. If the dose is very considerable the vessels of the muscles also react by contracting.⁴ In man the effect of adrenaline upon the skin vessels can be manifested by moistening a small area with adrenaline solution and passing a weak galvanic current inwards. This carries the adrenaline to the cutis vera, the vessels of which are intensely contracted and the area blanched (J. Graham Brown).⁵ The vessels of the conjunctiva are intensely contracted if adrenaline solution or extract of medulla is dropped into the eye (Oliver).

¹ J. Schmid, *Arch. f. d. ges. Physiol.*, cxxvi., 1909; Burton-Opitz, *Quart. Journ. Exper. Physiol.*, v., 1912, and vii., 1913; C. W. Edmunds, *Journ. Pharm. and Exper. Therap.*, vi., 1915; Macleod and Pearce, *Amer. Journ. Physiol.*, xxxv., 1914; Bainbridge and Trevan, *Journ. Physiol.*, li., 1917.

² Gradinescu, *Arch. f. d. ges. Physiol.*, clii., 1913; A. Krogh, *Journ. Physiol.*, liv., 1920; also *The Anatomy and Physiology of Capillaries*, 1922.

³ C. M. Gruber, *Amer. Journ. Physiol.*, xlv., 1918.

⁴ R. E. L. Gunning, *ibid.*, xliii., 1917.

⁵ Private communication.

Biedl and Wiesel¹ obtained a marked rise of blood-pressure in selachians, and Edwards² the same in the turtle from injection of adrenaline. Hartman, Kilborn, and Lang³ have investigated the effect of adrenaline on the vascular system of various vertebrates. In reptiles (snapping turtle) it caused only vaso-constriction, and relatively large doses were needed: in birds (common fowl) also only constriction: in marsupials (opossum) small doses produced a fall of blood-pressure, large doses a rise: in the goat the same: in the horse only a rise with all effective doses.⁴

ACTION ON THE PULMONARY CIRCULATION

Many observers have failed to obtain any effect on the pulmonary circulation, and have supposed that adrenaline has no action on the blood-vessels of the lung. Both O. B. Meyer⁵ and Argyll Campbell,⁶ however, obtained contraction of isolated rings of the pulmonary artery of the ox. It is, moreover, easy to show, both by perfusion of the vessels of the surviving lung (fig. 66) and by intravascular injections in the anæsthetised animal, that just as large a proportional effect may be obtained on the pulmonary blood-pressure by the action of adrenaline on the pulmonary arteries and right side of the heart as on the systemic arteries and left side of the heart (fig. 67).⁷

As in the systemic circulation, the rise in blood-pressure due to adrenaline has a double cause, viz. (1) contraction of blood-vessels; (2) increased action of heart. One or other of these may predominate. If the arteries of either system are intensely contracted by the autacoid, the amount of blood which passes to the other system will be restricted, the corresponding side of the heart will receive less blood, and therefore deliver less, and the blood-pressure will either not be raised or only slightly, and may even show a fall. A fall of pulmonary pressure may be produced by a minimal dose (fig. 68), as in the case of the aortic system⁸ (p. 118).

The idea that the pulmonary vessels are capable of little if any contraction, and differ in this respect from the vessels of the aortic system, is an error which M'Dowall suggests has arisen from the injury to those vessels and their nerve-endings caused when certain common anæsthetics, *e.g.* chloroform, are inhaled. As a matter of fact, the pulmonary arteries show well-marked contractility (both spontaneous and under the influence of hormones) which often takes on a rhythmic character, and may proceed to such an extent that in a lung which

¹ *Arch. f. d. ges. Physiol.*, xci., 1902.

² *Amer. Journ. Physiol.*, xxiii., 1914.

³ *Endocrinology*, ii., 1918.

⁴ E. D. Snyder finds that adrenaline differs in its effects according to the H-ion concentration of the solution. If this is above that of blood it acts as a depressor; if below, as a pressor agent (*Amer. Journ. Physiol.*, li., 1920, and lxii., 1922).

⁵ *Zeitschr. f. Biol.*, xlviii., 1906.

⁶ *Op. cit.*

⁷ Sharpey-Schafer and Lim, *Quart. Journ. Exper. Physiol.*, xii., 1919. The literature of the subject will be found in this paper.

⁸ Cf. E. M. Tribe (*Journ. Physiol.*, xlviii., 1914). Tribe finds that ergotoxine converts contraction into dilatation as in the systemic vessels.

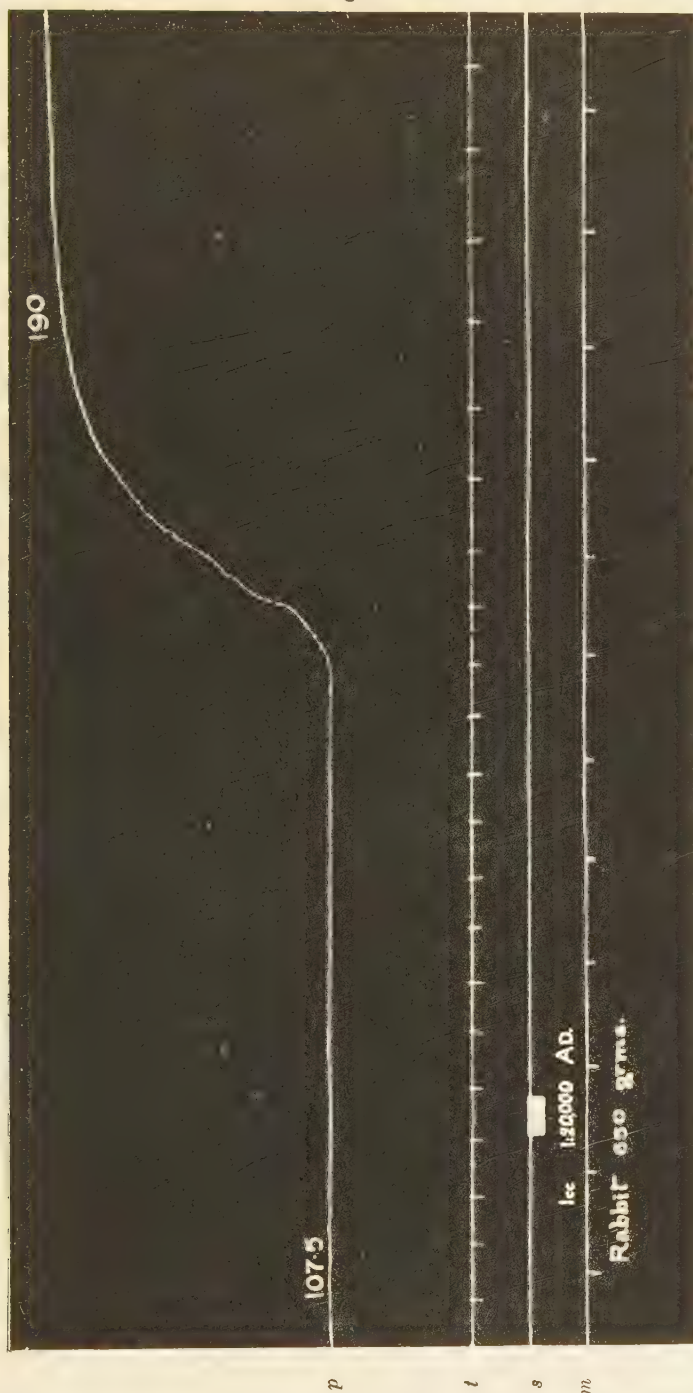


FIG. 66.—Experiment on surviving lungs of rabbit. Effect of adding to perfusion fluid 1 c.c. of 1 in 20,000 adrenaline chloride. Actual dilution 1 in 64,000. (Sharpey-Schafer and Lim.)

There is a marked constriction of the pulmonary arteries shown by the diminution in rate of outflow as measured by a "tilter" (line *t*), and by the rise of pressure central to the vessels (line *p*). Notice the wavy character of the rising pressure curve. *m*, time in minutes. The interval between the signal of injection (line *s*) and the commencement of the effect is occupied by the slow passage of the adrenaline through a coil of glass tubing used for warming the perfusion fluid to body temperature.

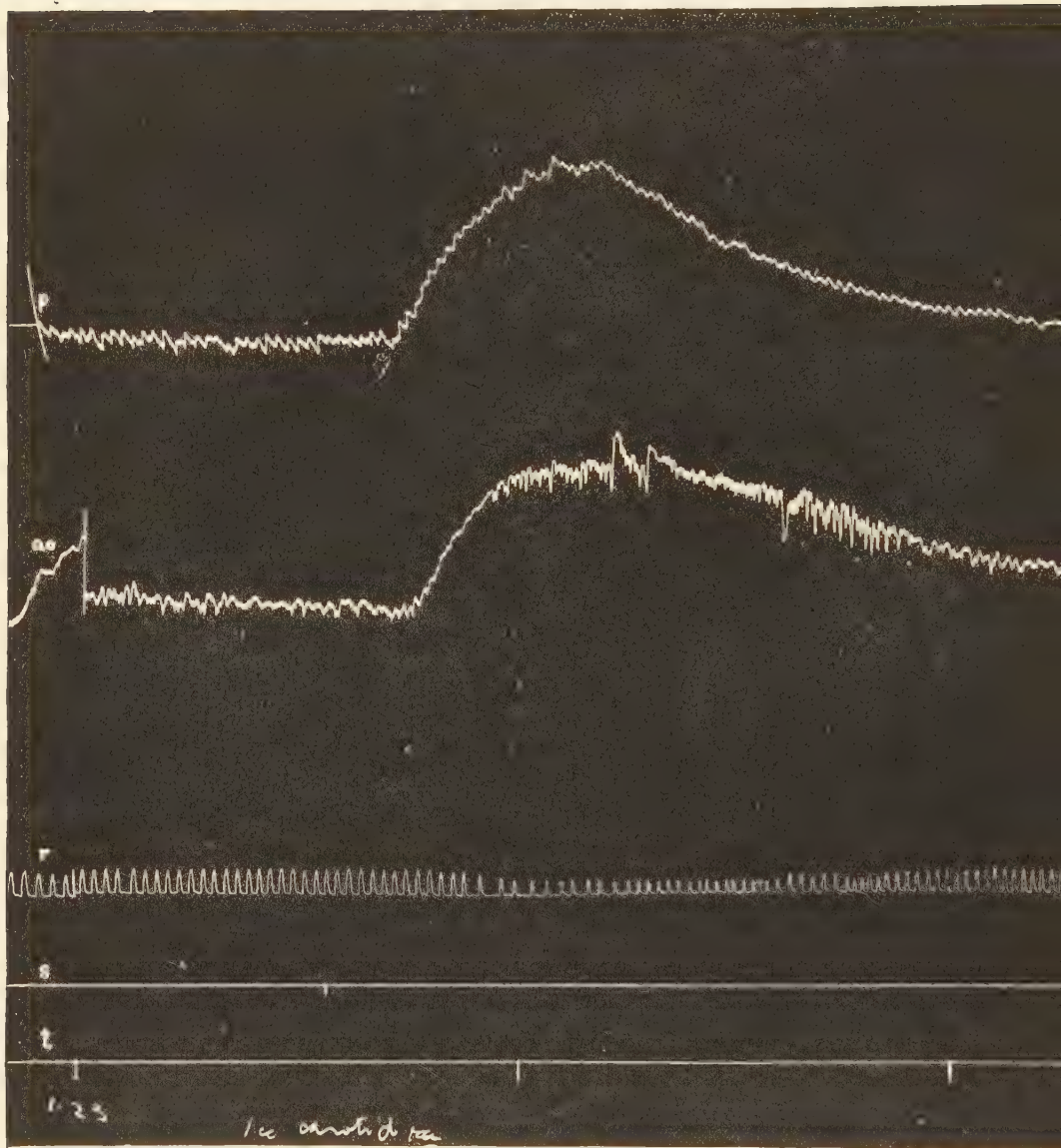


FIG. 67.—Cat. Effect of injecting 1 c.c. of 1 in 20,000 solution of adrenaline chloride into the aorta through a carotid. (Sharpey-Schafer and Lim.)

p, pulmonary blood-pressure (water manometer); *ao*, aortic pressure (Hg manometer); *r*, natural respiration; (notice the effect of the adrenaline upon them); *s*, signal; *t*, time in minutes. Simultaneous ordinates are seen on the left of the curves. The vagi had been cut in this animal.

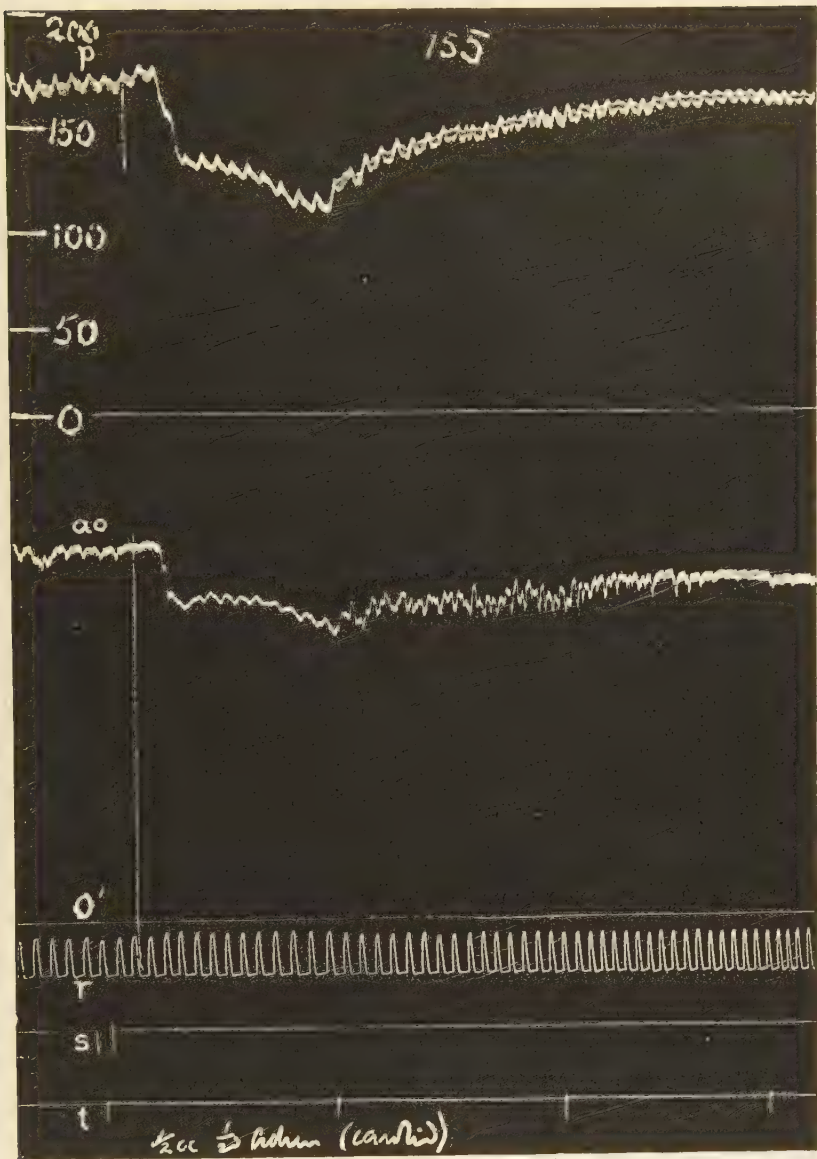


FIG. 68.—Cat. Effect on pulmonary and aortic pressures of injecting a minimal dose of adrenaline chloride into the aorta through a carotid. Vagi uncut. (Sharpey-Schafer and Lim.)
A scale in mm. of water-pressure is appended to the record of pulmonary pressure.

p , pulmonary pressure (water manometer); o , its zero; ao , aortic pressure (mercury manometer); o' , its zero;
 r , respiratory movements; s , signal; t , time in minutes.
Notice the fall in both curves due to vaso-dilatation, the heart rate being unaltered. The respiratory movements are at first slightly increased in extent.

is being perfused with Ringer's solution the flow may become rhythmically intermittent.¹

ACTION ON BLOOD-VESSELS OF OTHER ORGANS

With regard to the action of adrenaline on the blood-vessels of other organs, the most important results have been obtained upon the vessels of the *intestine*, of the *kidneys*, and of the *spleen*.

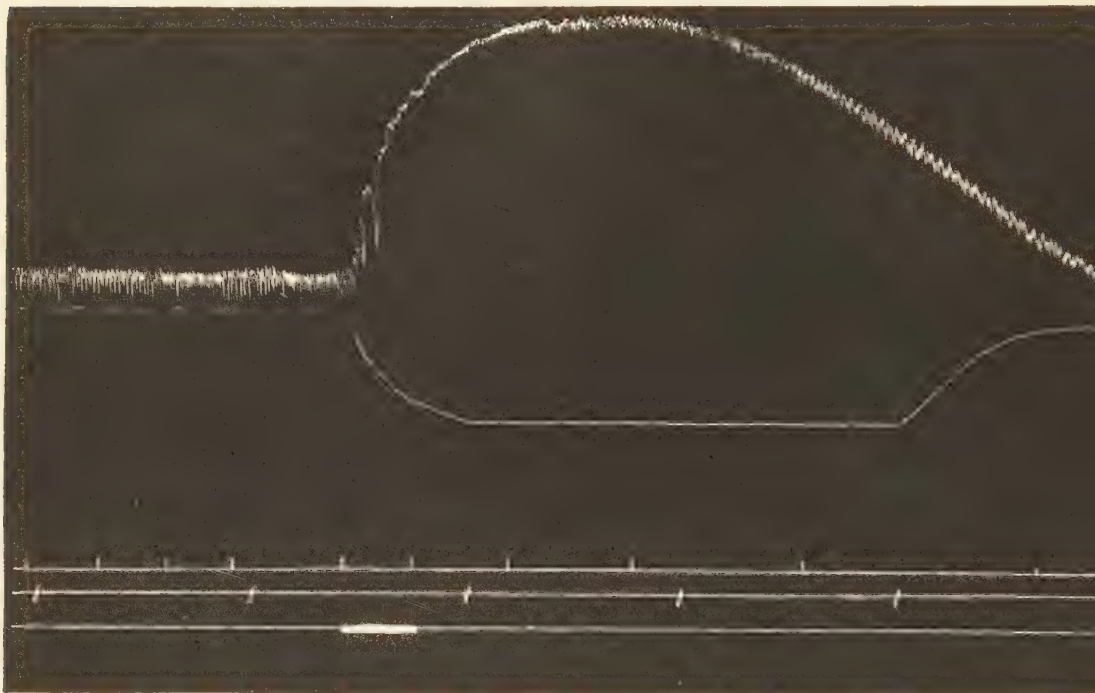


FIG. 69.—Effect upon blood-pressure, kidney volume, and flow of urine of injecting suprarenal extract into the vein of a dog. (From Schafer and Herring, *Phil. Trans.*, 1906.)

A, blood-pressure tracing; B, kidney volume change (oncograph): the full extent of the shrinkage is not recorded; C, drops of urine marked by magneto-electric signal; D, time in ten-second intervals; E, abscissa of blood-pressure and signal of injection.

With very small doses dilator effects are obtained in the arteries of the intestine, although with ordinary doses there is usually strong constriction.² Sometimes there is constriction followed by dilatation. The results have been obtained by direct observation, by plethysmography, by perfusion, or by measurement of venous outflow.

With the *kidneys* contraction of the organ in the plethysmograph, denoting

¹ R. J. S. M'Dowall, *Proc. Physiol. Soc., Journ. Physiol.*, lvi., 1922. Similar rhythmic contractions have long been known in systemic arteries. O. B. Meyer, *Zentr. f. Physiol.*, xxiii., 1909. See also H. Friedmann, *Arch. f. d. ges. Physiol.*, clxxxi, 1920.

² Oliver and Schafer, *op. cit.*, 1895; Brodie and Dixon, *Journ. Physiol.*, xxx., 1904; Fröhlich, *Zentralb. f. Physiol.*, xxv., 1911; Ogawa, *Arch. f. exper. Path. u. Pharm.*, lxxvii., 1912; Hartman and M'Phedran, *Amer. J. Physiol.*, xliii., 1917; R. G. Hoskins and Gunning, *ibid.*, 1917.

constriction of arteries, has usually been obtained with all doses (fig. 69),¹ but this is sometimes preceded or followed by dilatation usually regarded as passive. In a few cases, with extreme dilution, dilatation has been obtained. In perfusion experiments on the excised organ (fig. 70), and in ring experiments, Argyll Campbell always obtained constriction.² It is noteworthy that when adrenaline acts slowly, as in subcutaneous injections, diuresis is caused, but whether under these circumstances the kidney vessels dilate or whether the diuresis is provoked by contraction of the efferent vessels of the glomeruli is uncertain.

The *spleen* is one of the most sensitive organs to adrenaline (fig. 71). It contracts enormously with moderate doses, and very distinctly with minute

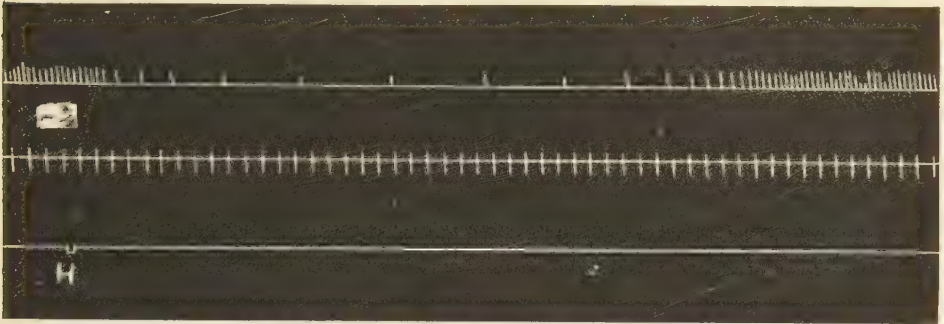


FIG. 70.—Effect of perfusing 10 c.c. of a 1 in 80,000 solution of adrenaline (hemisine) through the vessels of a surviving kidney (sheep). (Argyll Campbell.)

Each interval between the markings on the upper line represents the flow of 6·2 c.c. of the perfusing fluid (Ringer). At H on the signal line the adrenaline was added to the fluid flowing to and through the kidney. After its effect is produced, it gradually passes off as normal Ringer supplants it. The time markings on the middle line show half-minute intervals.

doses.³ The contraction, which involves not only the arteries, but also the muscular capsule and trabeculae, lasts long after the effect on the blood-pressure has returned to normal. Sometimes the contraction is preceded by dilatation,⁴ which may, however, be passive.

It must be borne in mind that dilatation is occasionally got from very weak stimulation of the splanchnics; these probably, therefore, contain some inhibitory fibres.⁵

¹ Oliver and Schafer, *op. cit.*, 1895; Bardier and Fraenkel, *Journ. de Physiol.*, i., 1899; R. Gottlieb, *Arch. f. exper. Path. u. Pharm.*, xliii., 1899; Sollmann, *Amer. Journ. Physiol.*, xiii., 1905; Schafer and Herring, *Phil. Trans.*, excix., 1906; Peri, *Arch. ital. de biol.*, xlv., 1906; D. Jonescu, *Wien. klin. Woch.*, 1908; Ogawa, *op. cit.*, 1911; Hartman and M'Phedran, *op. cit.*, 1917; Hoskins and Gunning, *op. cit.*, 1917; Hartman and Lang, *Endocrinology*, iii., 1919.

² *Op. cit.*

³ Oliver and Schafer, *op. cit.*; Bardier and Fraenkel, *op. cit.*; Hoskins and Gunning, *Amer. J. Physiol.*, *op. cit.*; Hartman and M'Phedran, *op. cit.* Subcutaneous injections will cause its contraction, and by forcing its blood into the general circulation increase the number both of erythrocytes and leucocytes in this.

⁴ R. G. Hoskins and Gunning, *op. cit.*

⁵ Schafer and Moore, *Journ. Physiol.*, xx., 1896.

The arteries to the *suprarenals* themselves are said to be contracted by adrenaline,¹ although, as Biedl showed, stimulation of the splanchnics causes an increased blood-flow from the veins.²

EFFECT OF ADRENALINE ON THE HEART

The effect of adrenaline on the *heart* is twofold—direct and indirect. The indirect effect is obtained by stimulation of the inhibitory vagus centre in

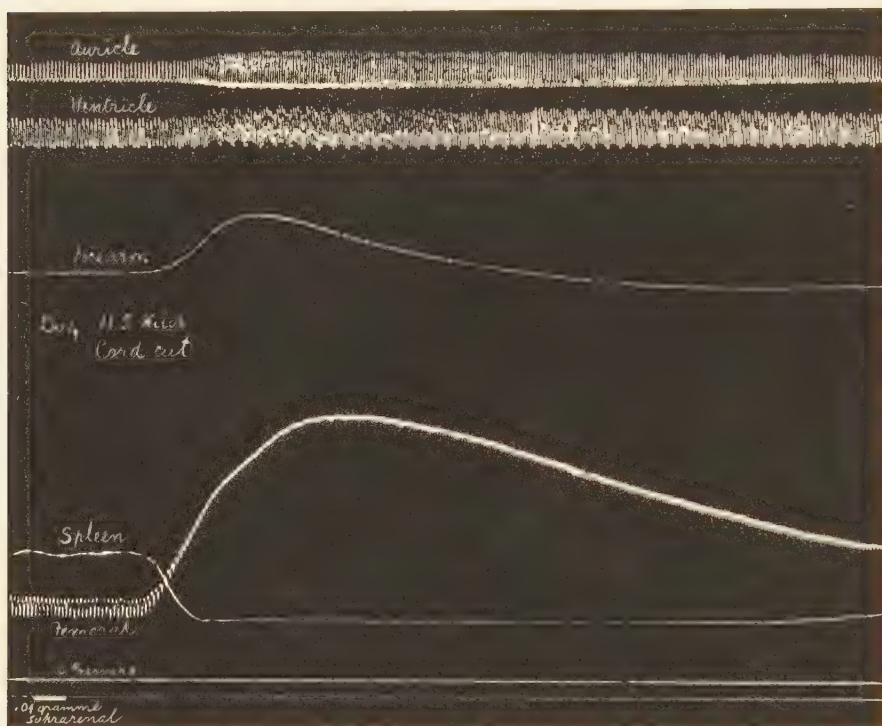


FIG. 71.—Contraction of spleen of dog as the result of injecting extract of suprarenal capsule (·01 gram) into a vein.

The spleen volume was recorded by an air-plethysmograph, the lever of which soon reached the limit of its registering capacity owing to the great contraction of the organ. The plethysmogram of the fore-limb shows expansion, which is either passive, or due to dilatation of the vessels of its muscles. The acceleration and augmentation of auricle and ventricle is well-marked.

the medulla oblongata, which produces slowing and even complete stoppage of the heart—at least of the auricles—for under such circumstances in mammals the ventricles continue to beat, although at a slower rate of rhythm than before (fig. 60). This effect is never got immediately, but always after the lapse of at least a few seconds—sometimes sooner, sometimes later. The cardiac inhibition manifests itself upon the blood-pressure curve by the greater amplitude

¹ Hallion, *C. r. soc. biol.*, 1921; Masuda, *Acta schol. med. Univ. Imp. Kioto*, v., 1922.

² *Arch. f. d. ges. Physiol.*, lxvii., 1897.

of the heart-waves. If the vagi are cut or paralysed by atropine, no slowing, but only acceleration and augmentation are produced (fig. 61). When the slowing occurs it is probably the result not of excitation of the cardio-inhibitory centre by the autacoid, but of constriction of arterioles in the medulla oblongata,¹ causing a diminished supply of blood to the vagal centre, which is thereby stimulated.² If there is also some effect upon the cardio-accelerator centre, it does not influence the result, for the denervated and isolated mammalian heart responds to the action of adrenaline quite as strongly as when its nerves are intact. This effect is due, as with the effect on the blood-vessels, to the direct excitatory action of adrenaline on cardiac muscular tissue, which, like other tissues supplied by the sympathetic, contains a substance ("excitable substance") which has become formed under the influence of sympathetic nerves, and responds to the action of adrenaline in the same way as when those nerves are artificially stimulated. In the case both of the blood-vessels and the plain muscular tissue of the viscera, which are also supplied by the sympathetic, two kinds of action are possible from its stimulation, viz. either increase or diminution of activity: hence, under differing circumstances and in different organs, either contraction or inhibition is caused both from stimulating the sympathetic nerves and also by the action of adrenaline. But in the heart only one effect is produced through the sympathetic, viz. increased activity, and this is, at least in mammals,³ the only result obtained by adrenaline. According to W. E. Dixon, this effect may be antagonized by apocodeine.⁴

P. W. Clough⁵ states that patients with high blood-pressure are more sensitive to adrenaline than others, and that it affects both heart and blood-vessels more.

The perfused mammalian ventricle reacts to adrenaline like the heart *in situ*, but often there is no acceleration of the rate (fig. 72A). According to Austoni,⁶ strong solutions produce acceleration and increase of tone: weak solutions only augmentation of force. Brodie and Cullis also got in the isolated rabbit's heart an increase of force without acceleration when the adrenaline was used in extreme dilution.⁷ Elliott found that in the tortoise and pigeon only the auricle is directly affected, whereas in mammals both auricles and ventricles are excited by adrenaline.⁸ The action of adrenaline can also be observed on the isolated

¹ Probably the same cause is responsible for the diminution in the respiratory movements produced by intravenous injection of adrenaline (see p. 115).

² Oliver and Schafer, *op. cit.* E. D. Brown got cardiac slowing on perfusing the vessels of the medulla oblongata with defibrinated blood containing adrenaline (*Journ. Pharm. and Exper. Therap.*, viii., 1916). He regards this as showing a direct action of adrenaline on the vagus centre.

³ Noël Paton and Watson (*Journ. Physiol.*, xliv., 1912) found that in the duck the effect of adrenaline is to cause decrease in the strength of the ventricular beats, which may more than compensate for the arterial contraction simultaneously produced, so that a fall of blood-pressure may result even with comparatively large doses. The contraction of the auricles is, however, augmented.

⁴ *Journ. Physiol.*, xxx., 1903.

⁵ *Johns Hopkins Hosp. Bull.*, xxxi., 1920.

⁶ *Arch. ital. de biol.*, lvi., 1911.

⁷ *Journ. Physiol.*, xliii., 1911. Cf. also T. R. Elliott, *ibid.*, xxxii., 1905, and Cleghorn, *Journ. Physiol.*, ii., 1899.

⁸ *Ibid.*, xxxii., 1905.

and perfused frog-heart, the force of the contractions being usually increased without apparent effect on the rate. The effect is influenced by the relative amounts of Ca and K in the perfusion fluid.¹ Occasionally there is a marked effect upon the tone of the cardiac muscle, which is increased by the action of the autacoid (fig. 72B). After perfusion with dibasic sodium phosphate, W. Burridge obtained a diminution of tone with adrenaline.²

The same observer, working with the isolated frog-heart perfused with Ringer's solution, finds that traces of adrenaline act like a lubricant to a machine, facilitating its action, and compensating for any defect of balance in the inorganic

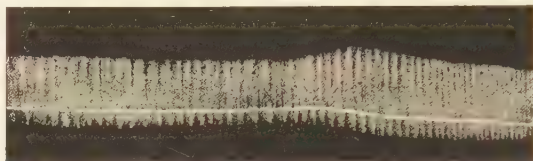


FIG. 72A.—Effect of adding a small amount of adrenaline to perfusion fluid (Locke) of isolated ventricle of rabbit.

The individual contractions cannot be seen in the reproduction, but their rate is not perceptibly increased although the extent of the movements is markedly greater. This is produced as much by increased dilatation as by augmentation of contraction. The waves on the curve appear to be due to fluctuations in tone of the muscle. It will be seen that the adrenaline has caused an increased rate of these fluctuations accompanied by a slight general fall in tone.

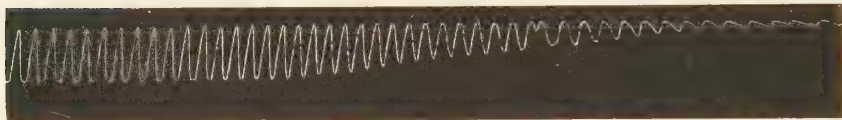


FIG. 72B.—Effect of adding adrenaline to Ringer's fluid used in perfusion of frog-ventricle. (Oliver and Schafer.)

Notice that the tone of the muscle is raised so that the heart passes into a condition of tonic contraction. The rate is not increased. The extract was added at X.

salts of the solution.³ J. A. Gunn,⁴ employing the perfusion method and the isolated heart of the rabbit or cat, found that, as regards the heart, adrenaline is a direct antagonist to most depressor substances, especially to chloroform and chloral (fig. 73). It will not—as was previously found by Schafer and Scharlieb⁵—revive a heart brought to a complete standstill by chloroform, although it will revive a heart which has been caused to stop by chloral. It must be regarded as a valuable means of restoring the heart's action in case of overdose of chloroform, and may in such cases be injected into the external jugular vein or even directly into the heart.

¹ Kolm and Pick, *Arch. f. d. ges. Physiol.*, clxxxiv., 1920; W. Liebrecht, *Arch. internat. de physiol.*, xv., 1920.

² *Quart. Journ. Exper. Physiol.*, v., 1912.

³ *Ibid.*, xii., 1920. See also *Quart. Journ. Exper. Physiol.*, x., 1917.

⁴ *Ibid.*, vii., 1914.

⁵ *Trans. Roy. Soc. Edin.*, xli., 1904. Cf. R. Gottlieb, *Arch. f. exper. Path. u. Ther.*, xxxviii., 1897, and xliii., 1899.

The heart's action can be caused to recommence even several hours after death if the coronary arteries are perfused with Locke's solution after Langendorff's method. This solution is, however, much more effective if a very small amount of adrenaline be added to it.

In Starling's heart-lung preparation in the dog, Lovatt Evans found that adrenaline causes great acceleration, with shortening of both diastole and systole, whilst in a similar preparation Anrep was able to show also an increase of tone

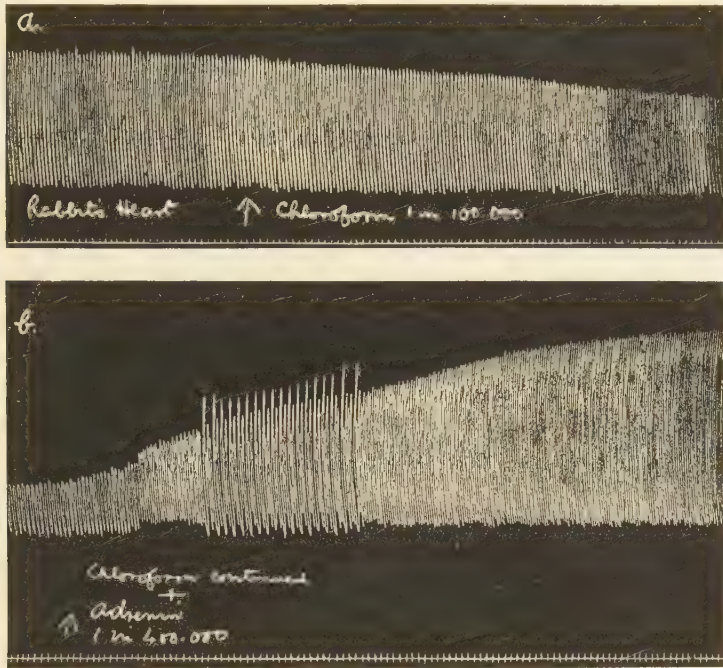


FIG. 73.—Revival of isolated ventricle by adrenaline after its action had been reduced by chloroform. (J. A. Gunn.)

a, beginning of perfusion with chloroform; b, two minutes later, showing effect of adding adrenaline to the chloroform solution (arrow).

in the cardiac muscle. The effect of adrenaline in such preparations is greatly to increase the metabolic processes, as shown by O_2 consumed.¹

The accelerating action of adrenaline is mainly produced through the auricle; if this is separated from the ventricle—as in heart-block—the acceleration of the ventricle is less marked, or may not appear, but the force of the ventricular contraction is always increased. A partial block may be removed by adrenaline.

Gruber and Markel² find that adrenaline, whilst increasing the rate and force of the heart-beats of the terrapin, causes diminution and disappearance of the tonus waves of the auricle. This obtains both in normal and in atropinised animals.

¹ Anrep, *Journ. Physiol.*, xlv., 1912; Evans and Ogawa, *ibid.*, xlvii., 1914; Evans, *ibid.*, li., 1917.

² *Journ. Pharm. Exper. Ther.*, xii., 1918.

CHAPTER XV

THE SUPRARENAL CAPSULES (*continued*)

EFFECT OF ADRENALINE ON PLAIN MUSCLE OF VISCERA

THE effect of adrenaline upon involuntary muscle is not confined to that of the vascular system. All other involuntary muscular tissue supplied by sympathetic fibres is also acted upon. This action may be *hormonic*, and take the form of increase of contraction and tonus, or *chaloneic*, and cause relaxation with inhibition of tonus. We may consider its action upon the several organs separately, since there are variations under different circumstances and in different animals.

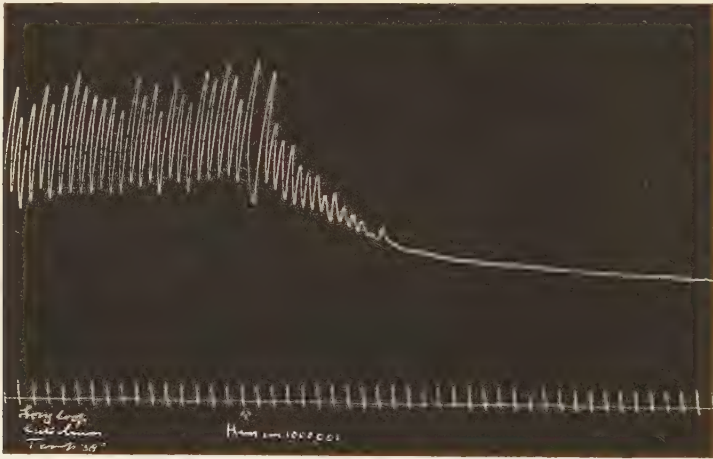


FIG. 74.—Effect of immersing a strip of the longitudinal coat of the ileum of a cat in one-in-a-million solution of adrenaline. (A. W. Young.) Time in 10 secs.

Alimentary Canal.—Adrenaline generally causes inhibition¹ of both the rhythmic movements and of the tonus of the plain muscle of the alimentary canal. This is used as one of the most delicate physiological tests for its presence in any fluid. According to R. Magnus² a strip from the longitudinal muscular coat of the cat's intestine is inhibited if immersed in Ringer's solution containing only 1 part of adrenaline in 20 millions: but Hoskins got inhibition of a piece of rabbit's intestine with a solution of 1 in 400 millions, and Stewart

¹ H. Boruttau, *Arch. f. d. ges. Physiol.*, lxxviii., 1899.

² *Ibid.*, cviii., 1905; and *Ergebn. d. Physiol.*, vii., 1908.

and Rogoff with 1 in 800 millions.¹ Occasionally the inhibition fails and is replaced by an excitatory effect. This has been noted by J. L. Bunch, by Magnus, and by Tashiro.²

R. G. Hoskins³ states that stimulation is only caused by doses which are below the threshold for producing inhibition. This is, however, certainly not always the case. I have myself obtained excitatory effects with all doses which yield any result (fig. 75). Similarly Bunch found that splanchnic

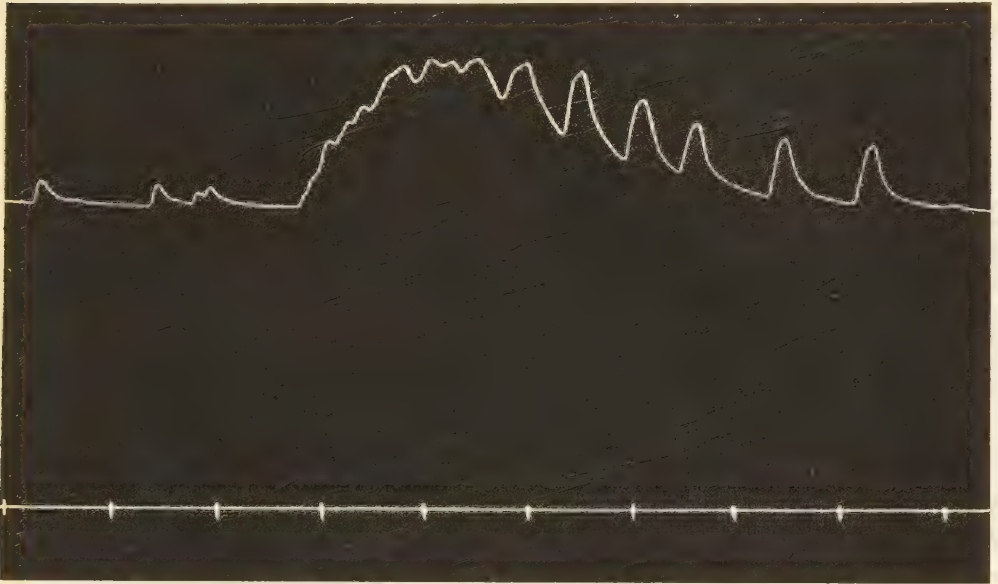


FIG. 75.—Effect of adrenaline in producing contraction of intestinal strip of cat. The amount of adrenaline chloride used was 1 c.c. of 1 in 100,000: it was diluted about five times before reaching the muscle. A solution of 1 in 10,000 gave a similar result.

stimulation, which usually causes inhibition, occasionally causes increased contraction of the intestine of the anæsthetised animal.⁴ It is, therefore, to be inferred that the splanchnics convey both inhibitory and excitatory influences to the plain muscular tissue of the alimentary canal, but that the fibres conveying the inhibitory impulses are either usually more numerous or their endings more sensitive—and that occasionally a reversal of the ordinary condition obtains.

Adrenaline causes excitation—not inhibition—of the *muscularis mucosæ*.⁵

¹ *Amer. Journ. Physiol.*, xlviii., 1919. The rhythmic contractions of the plain muscle of the chick's amnion are inhibited by adrenaline (J. N. Langley, *Journ. Physiol.*, xxxiii., 1905), although the amnion is not known to contain nerves.

² *Tokio Journ. Exper. Med.*, i., 1920.

³ *Amer. Journ. Physiol.*, xxix., 1912.

⁴ *Journ. Physiol.*, xxii., 1898.

⁵ Gunn and Underhill, *Quart. Journ. Exper. Physiol.*, viii., 1914; King and Arnold, *Amer. Journ. Physiol.*, lix., 1922. This is also an effect produced by stimulation of the sympathetic nerves.

In most animals the sphincters (pyloric, ileo-colic, and internal anal) are contracted—not relaxed—by adrenaline.¹ but the cardiac sphincter is relaxed (Langley). These again are sympathetic results.

In birds and amphibians adrenaline acts not as an inhibitor but as an excitant to the muscular tissue of the small intestine.² It produces relaxation of the œsophagus in amphibians, and of the large intestine of birds. These results correspond with the effects produced by stimulating sympathetic fibres.

The *gall bladder* is inhibited by adrenaline, but the *bile ducts* are contracted.

The muscular tissue of the bronchial tubes.—Almost all who have investigated the subject³ are agreed that adrenaline causes inhibition of the

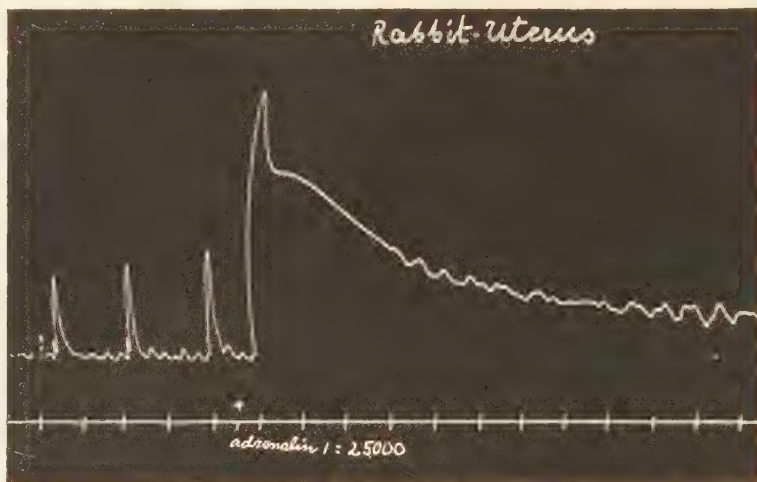


FIG. 76.—Effect of solution of adrenaline on cornu uteri of rabbit, the contraction of which is increased. (Itagaki.)

tracheal and bronchial musculature, and in conformity with this action it is in common use for the relief of bronchial asthma, given either by intramuscular injection or by the mouth.

The muscular tissue of the urinary and genital passages.—The *ureter* is stimulated by adrenaline, both in the rate of its rhythmic contractions and in its tone: but after ergotoxine inhibition is obtained.⁴

¹ T. R. Elliott, *Journ. Physiol.*, xxxi., 1904, and xxxii., 1905.

² According to C. M. Gruber strong solutions may cause relaxation, *Journ. Pharm. and Exper. Ther.*, xx., 1922.

³ Januschke and Pollack, *Arch. f. exper. Path. u. Pharm.*, lxvi., 1911; Trendelenburg, *ibid.*, lxix., 1912; Dixon and Ranson, *Journ. Physiol.*, xlv., 1912; E. A. Park, *Journ. Exper. Med.*, xvi., 1912; D. E. Jackson, *Journ. Pharm. and Exper. Therap.*, iv. and v., 1913–14. Golla and Symes (*ibid.*, v., 1913–14), who used an indirect method, thought that the bronchioles are at first constricted and afterwards inhibited by the autacoid. The experiments of Houssay show that adrenaline antagonizes the action of pituitrin upon the muscular tissue of the bronchioles, *Presse méd.*, 1918, p. 513.

⁴ D. I. Macht, *Journ. Pharm. and Exper. Therap.*, viii., 1916; Y. Satani, *Amer. Journ. Physiol.*, xlix., 1919; Wislocki and O'Connor, *Johns Hopkins Hosp. Bull.*, xxxi., 1920.

The effect on the *urinary bladder* varies with the species of animal—in this also the sympathetic effects, with slight variations, are imitated.¹ Most animals show very little effect; but in the monkey and cat the organ is relaxed. In the goat and ferret it is contracted; ² but relaxed after chryso-toxine (a derivation of ergot). Frequently the base is contracted and the fundus relaxed.³ Leo Adler⁴ obtained inhibition in the frog although sympathetic stimulation generally causes contraction.

The *urethra* is contracted in the cat (Elliott).

The *uterus* may be either stimulated (fig. 76) (most animals) ⁵ or inhibited

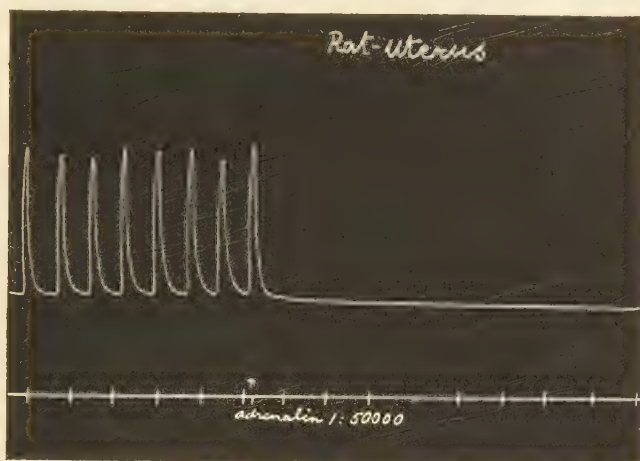


FIG. 77.—Effect of solution of adrenalin upon an isolated portion of uterus of rat. (Itagaki.) The contractions are inhibited.

(fig. 77) (rat, mouse, guinea-pig).⁶ In the cat it is inhibited in the non-pregnant, contracted in the pregnant animal.⁷

The rabbit's uterus is very sensitive to the action of adrenalin, and its contraction is often employed as a physiological test for minute amounts. It is said to be sensitive to 1 in 20 millions.

¹ Lewandowsky, *Centr. f. Physiol.*, xiv., 1900; J. N. Langley, *Journ. Physiol.*, xxvii., 1901; T. R. Elliott, *ibid.*, xxxii., 1905, and *Proc. Physiol. Soc., Journ. Physiol.*, xli., 1911.

² Also under some circumstances in the cat and rabbit.

³ H. H. Dale, *Journ. Physiol.*, xxiv., 1906.

⁴ *Arch. exper. Path. u. Pharm.*, lxiii., 1918.

⁵ Langley and Anderson, *Journ. Physiol.*, xix., 1895.

⁶ Kehrer, *Arch. f. Gyn.*, lxxxi., 1907; J. A. and J. W. C. Gunn, *Journ. Pharm. and Exper. Therap.*, v., 1914; Itagaki, *Quart. Journ. Exper. Physiol.*, xi., 1917. Will and Crawford (*Proc. Soc. Exper. Biol.*, xi., 1914) found that adrenalin causes in the guinea-pig uterus inhibition of the longitudinal muscle and contraction of the circular. They explain the difference in its action on the normal and gravid uterus by the greater hypertrophy of the circular fibres in pregnancy. But the Gunns got only inhibition.

⁷ H. H. Dale, *Journ. Physiol.*, xxxiv., 1906. See also A. R. Cushny, *ibid.*, xxxv., 1906; Dale and Laidlaw, *ibid.*, xlv., 1912; Backman and Lundberg, *C. r. d. réunion biol. de Suède*, lxxxvii., 1922. Botazzi obtained similar results in the bitch (*Atti d. r. acc. med.-chir. Napoli*, 1917). After ergotoxine only inhibition is obtained.

The muscular tone of the *vagina* is in some animals increased (dog, pig, rabbit, sheep), in others diminished (cat, cow, guinea-pig, rat).¹

The *vas deferens*, the *seminal vesicles*, and the *muscular tissue of the prostate* are all stimulated to active contraction by this autacoid.²

The *external genital organs* become smaller under the action of adrenaline. This may be due to contraction of their blood-vessels. The *retractor penis*, when present, is stimulated (Fletcher). The muscular tonus of the *dartos* is inhibited.

The *arrectores pilorum* are strongly excited in some animals : scarcely at all in others. As Elliott has pointed out, this depends largely upon the habit of the animal ; those which readily bristle up being most easily affected.³

Plain muscular tissue of the orbit and globe of the eye.—Müller's muscle of the orbit is contracted, so that the globe of the eye becomes more prominent and the palpebral aperture enlarges. This enlargement may be assisted by contraction of the plain muscle of the upper eyelid. The third eyelid in animals is retracted. All these are "sympathetic" effects. The *radiating fibres* of the iris contract, and the *sphincter* is inhibited, causing wide dilatation of the pupil.⁴ This effect is stronger and more prolonged after previous extirpation of the superior cervical ganglion and degeneration of its post-ganglionic fibres. Under these circumstances subcutaneous administration of adrenaline, or dropping adrenaline solution into the conjunctival sac is effective, or even administration by the mouth, none of which methods of administration produce the result in normal animals.⁵

If the enucleated eye of a frog is placed in Ringer's solution containing adrenaline, the pupil in a short time becomes widely dilated.⁶ This reaction will occur in a solution containing only 1 part adrenaline to 20 millions.

R. M'Carrison⁷ finds that adrenaline not only causes dilatation of the frog pupil, but in dilute solutions greatly increases the range of activity of the iris, this action being correlated with the H-ion concentration of the medium it is immersed in. The optimum is between 7.4 and 6.8 P_H. Above or below these limits the activity is lessened.

¹ J. A. Waddell, *Journ. Pharm. and Exper. Therap.*, ix., 1917.

² Langley, *Journ. Physiol.*, xxvii., 1901 ; Waddell, *Journ. Pharm. and Exper. Therap.*, viii. and ix., 1916.

³ The feathers of birds (Langley, *Journ. Physiol.*, xxx., 1903) and the quills of the hedgehog (Lewandowsky, *Arch. f. Physiol.*, 1900) are also caused to move by adrenaline. In man, gooseskin is readily produced (T. R. Elliott, *op. cit.*, 1905).

⁴ M. Lewandowsky, *Centrbl. f. Physiol.*, xii., 1898, and *Arch. f. Physiol.*, 1899 ; D. R. Joseph, *Amer. Journ. Physiol.*, xlii., 1917. A relatively large dose is required (Langley).

⁵ S. J. Meltzer and C. Auer, *Amer. Journ. Physiol.*, xi., 1904. It is stated by Loewi that in diabetes, whether produced by disease or experimentally, and also in exophthalmic goitre, the pupil will react to instilled solution of adrenaline without removal of the ganglion (*Arch. f. exper. Path. u. Pharm.*, lix., 1908). Loewy and Rosenberg (*Biochem. Zeitschr.*, lxxvii., 1914) believe that the phenomenon is due to hyperglycæmia, as it does not occur with phloridzin-diabetes, in which there is hypoglycæmia.

⁶ Meltzer and Auer, *op. cit.* ; R. Ehrmann, *Arch. f. exper. Path. u. Pharm.*, liii., 1905, and *Deutsch. med. Woch.*, 1909.

⁷ *Brit. Med. Journ.*, Jan. 1923.

EFFECT ON PIGMENT CELLS

Adrenaline causes contraction of the pigment cells (melanophores) of the frog¹—a sympathetic effect—but produces expansion (distal migration) of the pigment in the retinal pigment cells, whether the animals are kept in

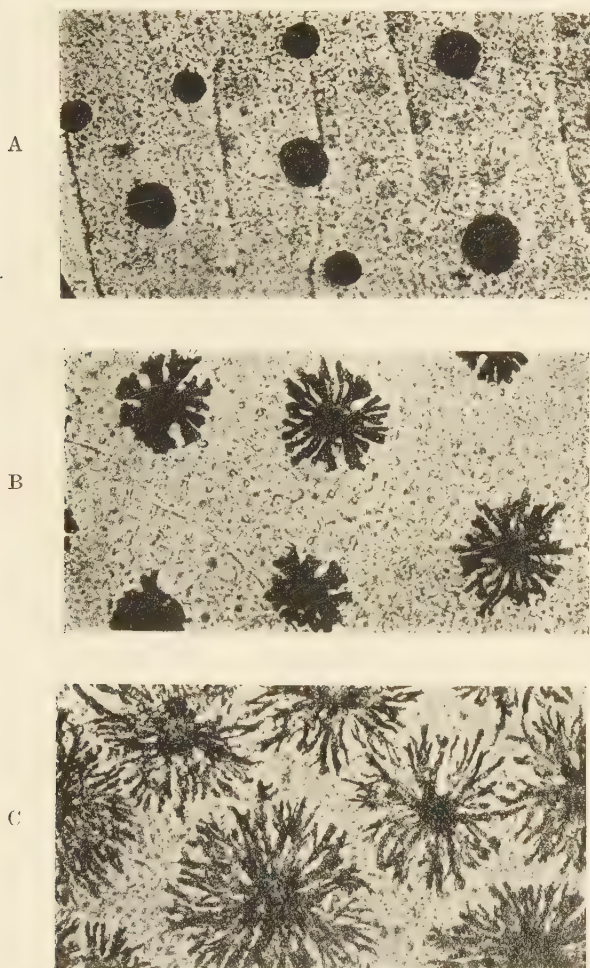


FIG. 78.—Melanophores of *Fundulus heteroclitus* (Spaeth and Barbour.)

A, effect of adrenaline; B, of ergotoxine alone; C, of adrenaline after ergotoxine.

the light or in the dark.² In fishes also (*Fundulus heteroclitus*) the skin melanophores (fig. 78) are contracted by adrenaline in all dilutions, down to

¹ Corona and Moroni, *Riforma medica*, 1898; van Rijnberk, *Ergeb. der Physiol.*, v., 1906. This effect can be seen under the microscope by painting adrenaline solution on the web (S. Lieben, *Zentr. f. Physiol.*, xx., 1906).

² Fujita, *Arch. f. vergl. Ophth.*, ii., 1911; A. J. Bigney, *Journ. Exper. Zool.*, xxvii., 1919; L. B. Arey, *Anat. Record*, xvi., 1919.

1:50 millions; but with prior administration of ergotoxine the contraction is replaced by expansion, as with the corresponding effects of the sympathetic stimulation.¹ Gilson² found that distal migration of the retinal pigment was caused in the same fish, but only in animals kept in the dark.

EFFECT ON GLANDS

Intravenous injection of adrenaline provokes the secretion of some of the externally secreting glands—those in particular which are known to be stimulated to secrete through the sympathetic.³

A flow of saliva from the submaxillary gland, similar to that caused by excitation of the cervical sympathetic, is produced by it, and is accompanied by contraction of the vessels of the gland. A larger dose of the autacoid is required than that necessary to raise the blood-pressure. The flow of saliva is less apparent in the dog than in the cat, in which animal, as is well known, excitation of the sympathetic in the neck provokes an abundant flow.

The salivary glands of the cat are singularly susceptible to the action of adrenaline after denervation, and any stimulation which tends to promote outpouring of adrenaline into the blood, whether a reflex one, such as that caused by excitation of an afferent nerve, or a direct one, such as excitation of the splanchnics, causes a marked increase in the flow of saliva.⁴

The *lacrimal glands* are caused to secrete, as well as the *mucous and serous glands* of the mouth, pharynx, gullet, windpipe, and bronchial tubes. These effects are accompanied by pallor due to vasoconstriction, followed shortly afterwards by flushing. The *sweat glands* are stimulated in the guinea-pig, but not in the cat. This is the usual statement, but Langley finds that adrenaline (0.001 per cent.) injected locally causes marked secretion of the glands of the cat's paw.⁵ The skin glands of the dog are caused to secrete.

Adrenaline has no effect on the *mammary gland*, and little or none on the glands of the *stomach* and *intestine*, or on the *liver* and *pancreas*. Such results as are obtained are in the direction of diminution of flow: this may be brought about by vascular constriction.

Kidney.—The effect of adrenaline on the kidney is twofold. The arteries of the kidney, and especially those of the glomeruli, contract strongly with all doses,⁶ and the result of this is to check or stop the secretion of urine for a time. But this effect presently passes off, and is replaced by increased

¹ Spaeth and Barbour, *Journ. Pharm. and Exper. Therap.*, ix., 1917. They regard these melanophores as homologous with plain muscle cells. For the literature, see v. Rijnberk, *Ergeb. der Physiol.* v., 1906, and Ballowitz, *Arch. f. d. ges. Physiol.*, clvii., 1914.

² *Proc. Nat. Acad. Sc.*, viii., 1922.

³ J. N. Langley, *Journ. Physiol.*, xxvii., 1901.

⁴ Florovsky, *Bull. de l'Acad. imp. d. Sci. Pétrograd*, 1917. This flow of saliva has been used by various observers to show the relative amount of adrenaline secreted under different circumstances, the number of drops per minute serving as an indicator.

⁵ *Autonomic Nervous System*, 1922, p. 80.

⁶ Schafer and Herring, *Phil. Trans.*, cxci., 1906; R. G. Hoskins and Gunning, *Amer. Journ. Physiol.*, xliii., 1918.

secretion. The increase is not due to increased blood-pressure, for this has fallen to, or even below, normal, but is probably a direct action of the autacoid on the renal epithelium; although it is possible, but not probable, that the efferent vessels of the glomeruli continue contracted after the rest of the blood-vessels have recovered their normal tone. Subcutaneous administration promotes diuresis. It increases the amount of urea excreted, whilst diminishing the amount in the blood.¹ In the perfused kidney the addition of adrenaline to the perfusion fluid causes increased secretion. Richards and Plant,² who furnish this statement, interpret it as an expression of more intense action on the vasa efferentia than on the vasa afferentia of the glomeruli. They obtain the same result even if the blood-flow is decreased, and in experiments on animals from which all the abdominal viscera except the kidneys are removed.

D. Cow³ found that, after one suprarenal had been removed and the vein from the other one tied, there may be a sufficient amount of adrenaline carried to the capsule of the kidney by a collateral circulation between the two organs to produce constriction of the cortical renal arteries and a diminution of the fluid which is excreted through the corresponding ureter. He considers that this collateral supply of adrenaline direct to the kidney would account for the results obtained by Asher and Pearce,⁴ who found that stimulation of the splanchnics—even in animals in which most of the abdominal viscera had been removed—caused diminution in the amount of urine secreted by the denervated kidneys, and stimulation of the vagus an increase, and explained these results as direct secretory and inhibitory effects on those organs. Cow expresses the opinion that the suprarenal bodies may be regarded as direct regulators of renal activity. In connexion with this the intimate anatomical connexion of suprarenals and kidney substance in Amphibia may be called to mind.

Internally secreting glands.—The externally secreting glands are not the only secreting structures stimulated by adrenaline: some of the internal secretions are also affected. This is probably the case with the thyroid, the secreting fibres of which are derived from the sympathetic, and may be true for the internal secretion of the pancreas. The liver under its influence discharges carbohydrate into the blood in the form of glucose.⁵ It is also found that the introduction of adrenaline into the blood stimulates the medulla of the suprarenals themselves so that the suprarenal veins contain a larger amount of the autacoid than under normal circumstances.

¹ Addis, Barnett, and Shevky, *Amer. Journ. Physiol.*, xli., 1918. In confirmation of Marshall and Davis (*Journ. Pharm. and Exper. Therap.*, viii., 1916) they found that decapsulation has the opposite effect.

² *Amer. Journ. Physiol.*, lix., 1922.

³ *Journ. Physiol.*, xlviii., 1914.

⁴ *Zeitschr. f. Biol.*, lxxxiii., 1913.

⁵ This must be through the nervous system, if it be the case, as Abelin and de Corral affirm, that addition of adrenaline to fluid which is being perfused through the surviving liver does not affect the glycogen-content of that organ (*Biochem. Zeitschr.*, lxxiii., 1917).

CHAPTER XVI

THE SUPRARENAL CAPSULES (*continued*)

RELATION TO THE SYMPATHETIC SYSTEM

IN most cases suprarenal extract only affects tissues which are supplied with nerves from the sympathetic system, and in the embryo in these tissues only after they have received their nerve supply.¹ It does not, however, act upon the nerves themselves nor on the nerve-endings, for severance of the nerves, so far from stopping the action, tends, on the contrary, to make the tissues supplied by the severed nerve, especially after its fibres have degenerated, more easily excited by the autacoid. This has been found to apply not only to the heart and blood-vessels, but also to the pupil, to the retractor penis, and to the salivary glands, and is probably of general application.

Although not entirely without exception, it may be stated that the effect of injecting extract of medulla of suprarenal (adrenaline) into the blood-vessels is the same as stimulating the sympathetic nerves throughout the body,² so that this autacoid may be regarded as a sympathetic excitant.³ It is concluded that under the influence of the sympathetic nerves the tissues produce, either at the junction of nerve and muscle (*neuro-muscular junction* (Brodie and Dixon), *myo-neural junction* (Elliott)), or throughout the cell-protoplasm, a material (*receptive or excitable substance* (Langley)), which reacts both with adrenaline and with other drugs, such as certain alkaloids. And it would, further, appear probable that this excitable substance increases either in amount or sensitivity after the action of the central nervous system and sympathetic ganglia is withdrawn by severance of the peripheral nerve.

Abolition of the effect of adrenaline in producing contraction of plain muscle (and the same applies to the effects of sympathetic excitation) can be obtained by administering ergotoxine—an amine base obtained from ergot, and also obtainable from the products of breaking down of histidine. Ergotoxine does not, however, paralyse the inhibition-producing effect of adrenaline, nor, it

¹ J. W. S. M'Fie, *Journ. Physiol.*, xxx., 1903.

² Langley, *Journ. Physiol.*, xxvii., 1901, and the *Autonomic Nervous System*, Part I., 1922; Elliott, *Journ. Physiol.*, xxxii., 1905.

³ In connexion with this it is interesting to bear in mind that the cells of the medulla of the suprarenal are derived from embryonic cells having a common origin with those of sympathetic ganglia. The parallelism between the action of adrenaline and the effects of stimulating sympathetic nerves, although not complete, shows but few exceptions. The subject is critically discussed by Langley in his *Autonomic Nervous System*, Part I., 1922, pp. 43 *seq.*

may be added, the inhibition caused by sympathetic excitation. Therefore, if, as often happens, either contraction or inhibition can normally be brought about under different circumstances through the sympathetic and also by adrenaline, when the normal effect is contraction, it is abolished by ergotoxine, the inhibition effect alone appearing, thus producing a reversal of the normal action. Where the normal effect is inhibition, it remains unaltered.¹ Dixon had previously obtained like results with apocodeine.²

Dale and Richards³ have cast doubt on the generally received idea upheld originally by Dale himself that these opposite effects are due to a double innervation from the sympathetic. This idea is based (1) on the fact that minimal doses of adrenaline often cause relaxation, and larger doses contraction; and (2) that after apocodeine and certain derivations of ergot, the contraction of the arteries (caused by adrenaline) with rise of pressure, is replaced by dilatation with fall of pressure. Dale and Richards state that dilatation is only got in carnivora, not in rodents nor in monkeys. They admit that the removal of skin from a limb will cause the shrinkage in the plethysmograph to be converted into swelling, but they explain this, not by supposing the vascular musculature to be inhibited, but to its having lost the reflex tonus from the skin and therefore no longer resisting passive dilatation from rise of pressure elsewhere. They consider the fall of blood-pressure which results from small doses of adrenaline to be due to an effect not on the arterioles but on the capillaries, resembling the action of histamine (β -imidazolylethylamine). This drug, although causing strong contraction of all plain muscle, nevertheless produces a fall of blood-pressure on intravenous injection,⁴ owing, it is believed, to its action in relaxing the capillaries and permitting a large amount of the blood to be retained in the capillary system. Such action contrasts with that of acetylcholine, which produces a fall by causing relaxation of the arterial musculature without directly affecting the capillaries. And the action of ergotoxine would be explained simply by its antagonism to the effect of adrenaline on the sympathetically supplied muscular wall of the arteries, so that the dilating action on the capillaries, which they suppose adrenaline to have, would then alone come into operation.

There are, however, considerations which are opposed to this explanation. In the first place, it has been shown that adrenaline causes *contraction* of the capillaries in the excised nictitating membrane of the frog's eye.⁵ Especially striking is the reversal caused by ergotoxine in structures other than the blood-vessels. One such example is supplied by the observations of Spaeth and Barbour on the skin melanophores of the fish, *Fundulus heteroclitus* (see p. 137), which are intensely contracted by adrenaline and intensely expanded by it after the action of ergotoxine. If, as Spaeth supposes, the melanophores are in reality modified smooth-muscle cells, they are obviously oppositely affected under the different conditions. For it is not a question merely of paralysis of the cell

¹ H. H. Dale, *Journ. Physiol.*, xxxiv., 1906.

² *Journ. Physiol.*, xxx., 1903.

³ *Ibid.*, lii., 1918.

⁴ Dale and Laidlaw, *Journ. Physiol.*, xli., 1910, and xliii., 1911.

⁵ J. Kukulka, *Zeitschr. f. exper. Path.*, xxi., 1920.

by ergotoxine. This drug produces some expansion, but the expansion produced by adrenaline after the action of ergotoxine is far greater than that caused by ergotoxine alone (fig. 78). And, with regard to the capillaries, it appears that the contraction of these is probably determined by the branched cells of Rouget,¹ which embrace the capillary wall, and by their contraction and expansion produce constriction and dilatation of the capillaries.² These capillo-motor cells are in all probability modified smooth muscle-cells, or are homologous with these; and as capillaries have numerous nerves distributed to them, it is probable that their movements occur, like those of melanophores, under the influence of the sympathetic.



FIG. 79.—Contractile cells of Rouget on the wall of a capillary of tail of salamander tadpole. (Vimtrup.)

a, an expanded cell; b, a partially contracted cell, which is causing the lumen of its capillary to be diminished; c, an erythrocyte.

There are other structures which are known to have a double innervation, in which ergotoxine produces a reversal of action by paralysing the contractor effect of adrenaline, and brings to view its relaxor effect. This is the case with the bladder of some animals, which is contracted in the ordinary way by adrenaline, but relaxed or inhibited after ergotoxine. Intestinal muscle is generally inhibited, but is sometimes caused to contract, by exciting the splanchnics: both effects are obtainable with adrenaline, although inhibition is far more common. The arterial musculature, which is usually contracted by immersion in adrenaline solution, is sometimes inhibited by that autacoid, and after the action of ergotoxine, contraction is always replaced by inhibition. Taking these and similar circumstances into consideration—as well as the fact that many, probably all, blood-vessels have a double nerve supply—the original view taken by Dale that the action of ergotoxine depends upon the paralysis of vasoconstrictor or hormoneic

¹ *Arch. de Physiol.*, v., 1873, and *C. r. ac. Sci.*, lxxviii., 1879.

² See Vimtrup, *Zeitschr. f. Anat. u. Entwickl.*, 1922, and A. Krogh, *The Anatomy and Physiology of the Capillaries*, 1922.

nerves, whilst leaving vaso-inhibitor or chalone nerves uninfluenced, appears to furnish the most reasonable explanation of the observed phenomena.¹

According to del Campo, the effect of adrenaline in causing vasoconstriction is weakened or prevented by depriving the perfusion fluid of calcium.² On the other hand, Noyons³ states that the vasoconstrictor effect of adrenaline is prevented by excess of calcium in the perfusing fluid. The difference may be one of relative amount of calcium.

Atropine also antagonises the action of adrenaline in producing contraction of perfused blood-vessels, and may convert constriction into dilatation.⁴

The action of adrenaline upon the terminal apparatus of the sympathetic system is common to a number of primary and secondary amines: the action has been termed *sympatho-mimetic* by Barger and Dale.⁵ The more nearly the structure of the amine approaches that of adrenaline the more marked is this action. A knowledge of these facts has led to the production of various synthetic drugs having similar properties. The chemical history of adrenaline furnishes, indeed, a striking illustration of the drug-like character of autacoids.

Although it is generally considered that the action of adrenaline is upon the terminal tissue elements, or upon the neuro-muscular excitable substance within them, there are not wanting experiments to show that a certain amount of the effect may be produced in ganglia in which the preganglionic fibres of the sympathetic form synapses with the cells giving origin to the post-ganglionic fibres. Thus it has been shown that a certain inhibitory effect can be obtained in the intestine on injecting adrenaline into the jugular vein of an animal in which the adrenaline-containing blood is not allowed to pass to the gut (which is separately perfused)—or by painting either the sympathetic ganglia or the dorsal root ganglia with adrenaline.⁶ In connexion with this it is to be remembered that there are endings of sympathetic fibres not only in the sympathetic ganglia but also in the dorsal root ganglia.

Elliott thought that adrenaline does not excite sympathetic ganglia, like nicotine, but only the tissues in which the sympathetic nerves end.⁷

It has been suggested that a minute quantity of adrenaline, although insufficient in itself to produce any noticeable effects, may serve to maintain or increase the irritability of sympathetic nerve-endings. But R. G. Hoskins⁸ finds that this is not the case, for animals deprived of suprarenals react as readily as normal animals to sympathetic excitation, and a continuous infusion of dilute adrenaline tends rather to depress than to increase the effect.

¹ F. A. Hartman (*Amer. Journ. Physiol.*, xxxviii., 1915), while concluding for the existence of both kinds of fibres in the limb arteries, thinks there may be only vasoconstrictors in the splanchnics. But it is unlikely that there is such an absolute distinction, although there are, probably, considerable variations in the allotment of the two kinds of fibres to different vascular areas.

² *Zeitschr. f. Biol.*, lxix., 1918.

³ *Abstract in Endocrinology*, vi., 1922.

⁴ Backman and Lundberg, *C. r. d. réunion biol. de Suède*, lxxxvii., 1922.

⁵ *Journ. Physiol.*, xli., 1910. See also G. Barger, *The Simpler Natural Bases*, 1914.

⁶ Hartman, Kilborn, and Fraser, *Amer. Journ. Physiol.*, xlv., 1918.

⁷ *Journ. Physiol.*, xxxi., 1904 (*Proc. Phys. Soc.*, p. xx).

⁸ *Amer. Journ. Physiol.*, xxxiv., 1914.

CHAPTER XVII

THE SUPRARENAL CAPSULES (*continued*)

RELATION OF THE SUPRARENALS TO SKELETAL MUSCULAR ACTION

IN the experiments of Oliver and myself in 1894 we investigated the effect of extracts of suprarenal upon the contraction of skeletal muscle both in the frog and mammal. This effect seemed to be a prolongation of the muscular contraction caused by a single stimulus. More recent experiments have, however, shown that in moderate dilution no such effect is seen,¹ and there is reason to believe that the result we obtained was due to the extracts having been made

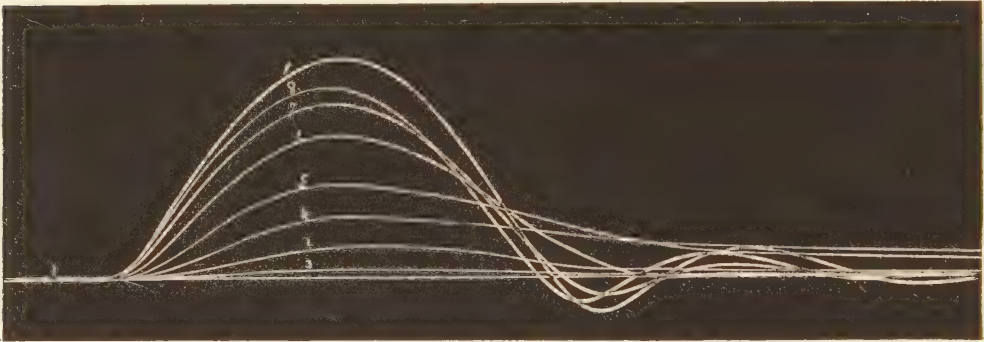


FIG. 80.—A series of eight successive curves of frog sartorius to show the effect of strong solution of adrenaline. (Takayasu.)

1, in normal Ringer; 2, after two minutes' immersion in 0.01 per cent. hemisine (adrenaline with addition of lactose); 3, after another two minutes in 0.01 per cent. hemisine; 4, 5, 6, 7, 8, successive curves showing gradual recovery on re-immersing and washing in normal Ringer. Curve 8 after 43 minutes in normal Ringer.

with glycerine, which has been shown to cause such prolongation.² In strengths of 0.0002 per cent. or over, adrenaline solutions have a certain effect upon the curve of contraction of muscle, but this effect is in the contrary direction and tends to cause a diminution in extent and in height. In stronger solutions (0.01 per cent.) the curves resemble those caused by fatigue (fig. 80).

That there is some relationship between the activity of muscles and the suprarenals would seem probable from the observations of Elliott and Tuckett,³

¹ Y. Kuno, *Journ. Physiol.*, xlix., 1915; Takayasu, *Quart. Journ. Exper. Physiol.*, ix., 1916. With very dilute solutions 0.0001 per cent., Okushima obtained an increase (*Acta schol. med. Kioto*, 1919).

² A. D. Rocha, *Bull. soc. Portug. d. sci. nat.*, viii., 1917.

³ *Journ. Physiol.*, xxxiv., 1906.

who found these glands to vary in size with the degree of muscular development of the individual. The muscular weakness in Addison's disease points in the same direction, and similar observations bearing out this inference have been recorded in animals. Thus R. G. Hoskins and Wheelon¹ found that after the suprarenals had been tied off in the dog the skeletal muscles became weakened in their action, and cardiac muscle also showed weakening, although the vascular musculature was not affected. On the other hand, adrenaline is passed in greater quantity into the blood during muscular work, for if in a cat one of the pupils was denervated by removal of the superior cervical ganglion, the pupil on the denervated side dilated when the animal was made to work a treadmill.² This effect failed after removal of the suprarenal capsules. The latent period was from 1.5 to 3 minutes. The effect passed off a few minutes after cessation of the exercise. Hartman found that the amount of work done is increased by intramuscular injection of adrenaline.

It is further found that adrenaline has the effect of postponing fatigue of muscle or of causing recovery from the effects of fatigue. If administered *in vivo* by the blood-flow in small doses, it causes dilatation of the vessels of the muscles and increased blood-flow; but the result is not wholly due to the increase of blood, for it will occur without any vascular change, *e.g.* in a denervated muscle the vessels of which are already dilated.³ Probably it acts by accelerating the metabolic processes, for Martin and Armistead⁴ find that the metabolism of excised frog-muscle (gauged by determination of P_H) is increased from 25 to 400 per cent. by adrenaline according to the concentration of the solution. The effect is not confined to muscle but is found also in other tissues and organs. Adrenaline is said not to increase the production of CO_2 .⁵ If a muscle is perfused and excited until fatigued, the addition of a small amount of adrenaline to the perfusion fluid greatly increases the extent of the (diminished) contractions.⁶ Nevertheless, adrenaline is not used up or removed from the circulation by contracting muscles.⁷

We have seen that white rats bear removal of both suprarenals without showing any definite symptoms for a long time. But it is stated that their liver-glycogen disappears, although it can be restored by feeding with sugar. Such animals are much more readily fatigued than normal animals—in this respect resembling patients afflicted with Addison's disease.⁸

¹ *Amer. Journ. Physiol.*, xxxiv., 1914.

² Hartman, with Waite, Powell, and M'Cordock, *Amer. Journ. Physiol.*, lx. and lxii., 1922; Hartman, *Endocrinology*, vi., 1922.

³ See on this subject a series of papers by C. M. Gruber in the *Amer. Journ. Physiol.*, from 1913 onwards. Cannon and Nice (*ibid.*, xxxii., 1913) found that fatigue was postponed in the muscles of a cat's limb if an excess of adrenaline was secreted, as by stimulation of splanchnic.

⁴ *Amer. Journ. Physiol.*, lix. and lxii., 1922.

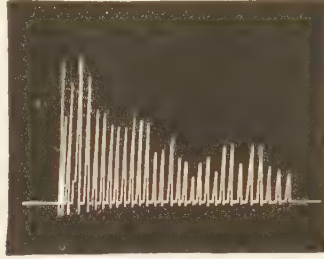
⁵ F. R. Griffith, *Amer. Journ. Physiol.*, lxiii. and lxv., 1923.

⁶ Guglielmetti, *Quart. Journ. Exper. Physiol.*, xii., 1919; *C. r. soc. biol.*, lxxxvii., 1922. Also Dessy and Grandis, *Arch. ital. de biol.*, xli., 1904, and Panella, *ibid.*, xlviii., 1907.

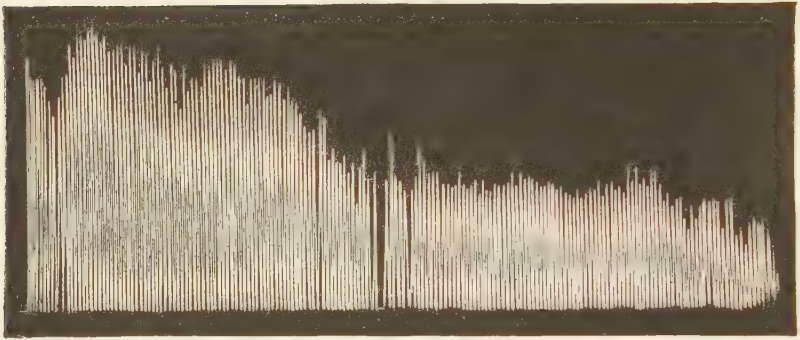
⁷ R. G. Hoskins and Durrant, *Proc. Amer. Physiol. Soc.*, *Amer. Journ. Physiol.*, lxiii., 1923.

⁸ O. Schwarz, *Arch. f. d. ges. Physiol.*, cxxxiv., 1910; E. Mauerhofer, *Zeitschr. f. Biol.*, lxxiv., 1922.

Adrenaline not only restores the irritability of fatigued muscle, but also increases the irritability of normal muscle. It also increases the height of the contractions both of fatigued and normal muscle when poured out into the blood by splanchnic stimulation.¹ Lucien and Parisot² find that adrenaline has the effect of postponing the onset of fatigue in frog-muscle. It will even



A



B

FIG. 81.—A, ergograph tracing from a person suffering from Addison's disease. B, tracing from the same person after six weeks' administration of suprarenal. (Langlois.)

A, natural size; B, reduced to one-half.

antagonise the fatigue effects produced in muscle by lactic acid or phosphate, and may restore the irritability of muscle which is apparently dead.³ This is strikingly the case with cardiac muscle. Even when suprarenal extract is given by the mouth it is said that the fatigue of muscle is less easily produced; this was found by J. P. Langlois⁴ to be the result in some cases of Addison's disease (fig. 81).

¹ C. M. Gruber, *Amer. Journ. Physiol.*, lxi. and lxii., 1922.

² *Les glandes surrénales*, 1913.

³ Gruber and Fellows, *Amer. Journ. Physiol.*, xlv., 1918.

⁴ *Presse méd.*, 1896; *Les capsules surrénales*, *Trav. d. Lab. Ch. Richet*, 1897.

CHAPTER XVIII

THE SUPRARENAL CAPSULES (*continued*)

EFFECTS OF SUBCUTANEOUS AND BUCCAL ADMINISTRATION

SUBCUTANEOUS injection of adrenaline does not produce the rapid effect on involuntary muscle which is so characteristic of intravenous injection—although intramuscular injection may do so.¹

In man the subcutaneous injection of a dose of from 0.5 to 1.5 mg. of adrenaline causes within a few minutes a slight elevation of arterial pressure, with pallor of the face and extremities produced by peripheral vasoconstriction. The effects vary, however, in different subjects; some being more, other less sensitive to small doses of the autacoid. In those subjects in which pallor of the face is produced, the pulse-oscillations of the small arteries, especially the radial, become gradually of less amplitude, until within a period of from forty-five minutes to one and a half hours they have almost disappeared, reappearing in the same gradual manner as the effect of the autacoid passes off.² The rise of blood-pressure, although slow in appearing, is long lasting: it is accompanied by a quickening of the pulse.³

Large hypodermic doses of suprarenal extract, or of the separated medulla, produce in rabbits and most other animals serious or even fatal symptoms.⁴ After a preliminary period of excitement, with rapid pulse and respirations, a period of depression supervenes. Accompanying this depression the muscular movements are first slowed; there is then paralysis of the limbs, and later of the respiratory muscles, with asphyxial convulsions. The body temperature becomes lowered some little while before death. The paralysis is central. Post-mortem, a general hyperæmia of the viscera is evident, and abundant hæmorrhages are seen to have occurred in various parts. If a first dose is not fatal, a certain amount of immunity may be produced to a subsequent dose (Vincent).

Various appearances have been described in organs resulting from chronic adrenaline poisoning. The chief of these are in the kidneys (inflammatory changes with desquamation of the cells of the convoluted tubules), and in the lungs (extreme congestion with œdema, which may proceed so far as to produce asphyxia).⁵

The minimal lethal dose of adrenaline given subcutaneously is from 10–20 mgs. per kilo. body weight. Administered intravenously it is in most animals

¹ S. J. Meltzer, *Berlin klin. Woch.*, 1911.
² Sines, 1921, p. 96.

³ Falta, Newburgh, and Nobel, *Zeitschr. f. klin. Med.*, lxxii., 1910.

⁴ Foà and Pellacani, *Arch. ital. de biol.*, iv., 1883; Oliver and Schafer, *op. cit.*; Swale Vincent, *Journ. Physiol.*, xxi., 1897; Elliott and Durham, *ibid.*, xxxiv., 1906.

⁵ Drummond, *Journ. Physiol.*, xxxi., 1904.

about 0.1 to 0.25 mg. per kilo., but in cats 0.5 to 0.8 mg. Administered orally it is not poisonous.

Feeding with suprarenal seems to have very little effect on the general growth of the body or on most organs, but the generative glands, especially the testes, are generally found to be larger in suprarenal-fed animals (rats) than in controls.¹ Probably this effect is due to cortical substance (see p. 105).

Considerable amounts of the extract of medulla or of adrenaline can be taken by the mouth without producing any such immediate physiological result as is caused by intravenous injection. This is probably due to the fact that the active material, although not destroyed by gastric juice, is absorbed but slowly and becomes destroyed in the tissues as fast as it is absorbed. That such destruction is readily produced is obvious from the fact that even when large doses are injected into a vein the effects pass off within a few minutes. Where the destruction occurs is not known, although it is probably in the tissues, but not necessarily those which it excites.² It was found by Oliver and myself that the active principle of the medulla when added in quantity is not destroyed by prolonged contact with blood. But Embden and von Fürth,³ using less of the autacoid, have been able to show that there is some diminution if it is kept mixed with arterial blood. This is, however, not enough to account for the disappearance of large quantities within a few minutes.⁴ It is not eliminated by the urine.⁵ Meltzer⁶ finds that it is destroyed by cerebro-spinal fluid. Since it has been shown that the autacoid is rapidly inactivated *in vitro* by dilute formaldehyde, it may be that the inactivation *in vivo* is brought about by this substance, which is believed to be one of the intermediate products of protein metabolism.⁷

Since adrenaline, when injected intravenously, even in quantity, rapidly disappears from the blood, it is not surprising that the small amount which might be constantly passing into that fluid from the suprarenals should not be capable of detection in the general blood-stream, in which it would of course become greatly diluted. Even in the blood of the inferior vena cava, just beyond (above) the orifices of the suprarenal veins, Abelous and Soulié⁸ failed to detect it.

¹ R. G. and A. D. Hoskins, *Arch. int. Med.*, xvii., 1916.

² Cf. T. R. Elliott, *Journ. Physiol.*, xxxii., p. 451, 1905; and A. L. Tatum, *Journ. Pharm. and Exper. Therap.*, iv., 1912.

³ Hofmeister's *Beitr.*, iv., 1904.

⁴ Trendelenburg was unable to detect it by the frog-perfusion method even after a large dose administered intravenously (*Arch. f. exper. Path. u. Pharm.*, lxiii., 1910).

⁵ Oliver and Schafer, *op. cit.* Falta and Ivcovič (*Wien. klin. Woch.*, 1909) state, however, that it can be detected in the urine after subcutaneous injection of large doses.

⁶ *Proc. Soc. Exper. Biol.*, ix., 1911.

⁷ W. Cramer, *Proc. Physiol. Soc.*, in *Journ. Physiol.*, xlii., 1911. No other autacoid is inactivated by this means. Oxidising agents, such as H_2O_2 , only very slowly affect its physiological activity, although producing an intensely red colour (Abderhalden and Gellhorn, *Arch. f. d. ges. Physiol.*, cxcix., 1923).

⁸ *C. r. soc. biol.*, April 8, 1922. According to these authors, blood serum has an inactivating action on adrenaline, which is not seen with blood plasma. But they appear to have used formalised horse serum, and this may have vitiated the result (Doyon, *ibid.*, lxxxvii., 1922).

Effects on Metabolism.—Subcutaneous injection of adrenaline was found by F. Blum¹ to produce hyperglycæmia and glycosuria. Although this is largely produced by mobilisation of the liver glycogen, and is more intense the greater the amount of stored glycogen, it occurs even if the animal had been fed on a diet free from carbohydrates: it is then accompanied by increased excretion of nitrogen.² This observation seems to indicate that under these circumstances the sugar is formed from protein.

But, according to Herter and Richards,³ glycosuria does not occur if the liver glycogen has been got rid of by the combined effects of fasting and phloridzin injection. L. Pollak⁴ states that in rabbits, the liver of which has been rendered glycogen-free by fasting and administration of strychnine, adrenaline may, when given in repeated doses, cause glycogen to be again stored in that organ, although it disappears from the muscles. According to A. J. Ringer, Dubin, and Frankl,⁵ adrenaline is able to mobilise and get rid of residual glycogen from the tissues (muscle) even after as much as possible has been removed by phloridzin. It is stated that the hyperglycæmia and glycosuria caused by adrenaline injection can be prevented by pituitrin or by ergotoxine.⁶ It can also be prevented by insulin.⁷

The ability of the organism to utilise dextrose is not impaired by adrenaline, the glycosuria which it produces having nothing to do with diabetes. Repeated doses of adrenaline eventually fail to cause further glycosuria.⁸

With a dose of 1 mgr. injected subcutaneously the hyperglycæmia begins to show itself in man within a few minutes, reaches its maximum in about an hour, and has disappeared after two to three hours. The increase of sugar in the blood produced by this amount of adrenaline is about 0.058 per cent. in normal individuals. With such a dose glycosuria is rarely obtained (only in 4 cases out of 35), although hyperglycæmia is always produced. When glycosuria occurs the sugar in the urine does not run parallel with the increase of blood-sugar, but begins to appear about three hours after injection, reaches its maximum two hours later, and has disappeared after about eleven hours.⁹

The hyperglycæmia is subsequently followed by a phase of hypoglycæmia.¹⁰

Intravenous injection of adrenaline is not only quicker in producing

¹ *Deutsch. Arch. f. klin. Med.*, lxxi., 1901.

² Noël Paton, *Journ. Physiol.*, xxix., 1903. Cf. Underhill and Closson, *Amer. Journ. Physiol.*, xvii., 1906.

³ *Med. News*, lxxx., 1902.

⁴ *Arch. f. exper. Path. u. Phar.*, lxi., 1909. See also A. Phocas, *C. r. soc. biol.*, lxxx., 1917. A similar result was obtained by Drummond and Paton (*Journ. Physiol.*, xxxi., 1904), in chronic adrenaline poisoning.

⁵ *Proc. Soc. Exper. Biol.*, xix., 1921.

⁶ E. Laurin, *Biochem. Zeitschr.*, lxxxii., 1917.

⁷ E. C. Noble, quoted by J. J. R. Macleod, Address to Physiological Congress, Edinburgh, *Quart. Journ. Exper. Physiol., Suppl. Vol.*, 1923.

⁸ Underhill and Closson, *op. cit.*, 1906.

⁹ Brösamlen, *Deutsch. Arch. kl. Med.*, cxxxvii., 1921. Brösamlen got hyperglycæmia and glycosuria from adrenaline more readily in exophthalmic goitre, and less readily in myxœdema. In diabetic cases there was no constant effect on the blood-sugar: sometimes a rise, sometimes a fall, sometimes no change.

¹⁰ Petényi and Lax, *Biochem. Zeitschr.*, cxxv., 1921.

glycæmia and glycosuria but is more effective than subcutaneous administration. A considerable hypodermic dose is required, according to Drummond and Paton and Brösamlen,¹ to produce glycosuria in man, but Bierry found 0.0001 gram per kilo. body weight to be sufficient.²

Section of the splanchnics does not prevent the effect.

Barcroft and Dixon found that the O_2 consumption of the surviving heart was greatly increased under the action of adrenaline.³

Wilénko⁴ states that addition of adrenaline to Locke's perfusion fluid (which contains glucose) used for the isolated heart of the rabbit considerably raises the consumption of sugar; but if the animal had previously received an injection of adrenaline the sugar consumption of the isolated heart is greatly reduced.

Lovatt Evans,⁵ working with the isolated heart-lung preparation, and using Locke's solution with glucose, found that when the rate of heart-beat is accelerated by adrenaline there is not only a greater consumption of oxygen per unit of time but also a greater consumption per beat. He regards this as due to a specific effect of adrenaline on metabolic changes in the tissue. The rise in CO_2 output was somewhat later than the O_2 intake. The respiratory quotient was, on the whole, unaltered.

The administration of adrenaline also causes increased metabolism of fats and proteins, especially when given to fasting animals.⁶ D. Marine finds that it causes increased O_2 consumption in both normal and thyroidectomised rabbits, but in the operated animals this is delayed in onset and lasts less time.

In normal individuals there is an increase of basal metabolism, commencing from a few minutes to half-an-hour after subcutaneous injection, and lasting one or two hours.⁷

Adrenaline produces a rise in body-temperature, with increased heat production.⁸ It also exercises a thermogenic effect on excised tissues, besides increasing their output of CO_2 in a remarkable manner.⁹ Injected into animals in small amounts, it both increases the rate of heat production and raises the respiratory quotient. According to Biedl, the rise of heat production only occurs in well-fed

¹ *Op. cit.*

² *Presse méd.*, xlvii., 1913.

³ *Journ. Physiol.*, xxxv., 1906. Barcroft and Piper obtained a similar effect with the salivary glands (*ibid.*, xlv., 1912).

⁴ *Arch. f. exper. Path. u. Pharm.*, lxxi., 1913.

⁵ Evans (with Ogawa), *Journ. Physiol.*, xlvii., 1914; *Proc. Physiol. Soc., Journ. Physiol.*, vol. xlix., 1915; *Journ. Physiol.*, li., 1917.

⁶ Underhill and Closson, *op. cit.*, 1906; Eppinger, Falta, and Rudinger, *Zeitschr. f. klin. Med.*, lxvi. and lxvii., 1908 and 1909.

⁷ I. Sandiford, *Endocrin.*, iv., 1920.

⁸ On heat production from subcutaneous injection of adrenaline, see I. Sandiford, *Amer. Journ. Physiol.*, li., 1920. Marine and Baumann (*Journ. metabolic Res.*, ii., 1922) obtained a prolonged rise in heat production from adrenaline administration in 27 out of 33 rabbits in which the suprarenals had been removed, and in 6 out of 15 in which they had been frozen with ethyl chloride. Previous thyroidectomy prevented this increase of heat production.

⁹ Boothby and Sandiford, *Amer. Journ. Physiol.*, li., 1920, lv., 1922, and lvi., 1923; Martin and Armistead, *ibid.*

animals: in starving animals there is diminution of heat production.¹ Crile, Rowland, and Wallace found that hypodermic injection of adrenaline produces a rise in temperature of the brain. They also observed a rise during asphyxia.²

M. L. Menten³ believes that adrenaline plays an important part in assisting the combination of O₂ with hæmoglobin in the pulmonary vessels, a view which has been strenuously advocated by Sajous.⁴

¹ Proc. XIth International Physiological Congress, *Quart. Journ. E per. Physiol. Suppl. Vol.*, 1923.

² *Amer. Journ. Physiol.*, lxvi., 1923.

³ *Ibid.*, xlv., 1917.

⁴ *Endocrinology*, ii., 1918.

CHAPTER XIX

THE SUPRARENAL CAPSULES (*continued*)

EVIDENCES OF THE PASSAGE OF ADRENALINE INTO THE BLOOD

THAT the passage of adrenaline into the blood is always proceeding in sufficient amount appreciably to raise the tone of the blood-vessels seems doubtful. It was found by Oliver and myself¹ that even in the blood of the suprarenal vein of the dog there may be normally not enough to cause a rise of blood-pressure when a few cubic centimetres are slowly injected into a vein.² But it is possible by employing more delicate physiological tests to obtain evidence in some animals of its presence in the suprarenal vein, and under certain circumstances in the blood generally.

The physiological tests for adrenaline depend upon its reaction with various forms of involuntary muscle. 1. The most delicate qualitative test appears to be the inhibition of intestinal muscle (p. 132). Cannon claims to have obtained a recognisable result with a solution of 1 in 400 millions, and Stewart and Rogoff with 1 in 800 millions. 2. The effect on the heart and blood-vessels of a mammal (cat or rabbit) is less delicate, but better for some purposes (fig. 82).³ The animal should be pithed or the brain destroyed, and artificial respiration maintained: a manometer is connected with an artery; the injections are made into a vein, all under the same conditions. The vagi should be cut, or paralysed with atropine. Under these circumstances as small an amount of adrenaline as 0.0003 mg. per kilo. body-weight will cause a distinct rise of arterial pressure in the rabbit and an increase of rate and force of the heart's action.⁴ A number of successive injections of different fluids to be tested can be made: each will cause a rise proportionate to the amount of adrenaline if the blood-pressure is on the same level to start with in each case.⁵ Moreover, there is a certain amount of sensitisation produced as the result of successive doses—this must also be taken into account.⁶ 3. The effect of perfusion through

¹ *Op. cit.*, 1895.

² Confirmed by G. N. Stewart (*Journ. Exper. Med.*, xiv. and xv., 1911 and 1912), and by Gley and Quinquaud (*Journ. de physiol.*, xvii., 1915). Only with massage of the gland or on stimulating its nerves could evidence of the presence of adrenaline be obtained by these authors.

³ T. R. Elliott, *Journ. Physiol.*, xlv., 1912. The blood-pressure action seems to have been first suggested for quantitative estimations by E. M. Houghton, *Amer. Journ. Pharm.*, lxxiii., 1901; *Journ. Amer. Med. Ass.*, xxxviii., 1902.

⁴ I. D. Cameron (with Paton), *Proc. Roy. Soc. Edin.*, xxvi., 1905. Cameron finds that 0.69 gram of nitroglycerine is exactly antagonised by 0.0075 mg. adrenaline, and suggests that this may be used as a quantitative test.

⁵ D. Murray Lyon, *Journ. Pharm. and Exper. Therap.*, xxi., 1923.

⁶ Lieb and Hyman, *Amer. Journ. Physiol.*, lxiii., 1922.

the blood-vessels of a recently killed frog.¹ Adrenaline by its action on the vessels affects the rate of flow of the perfusion fluid. 4. The effect upon the excised uterus of the rat, which is inhibited by this autacoid, or of the rabbit, which is stimulated. The non-pregnant uterus of the cat was also found by Dale and Laidlaw to be inhibited by 1 part in 20 millions Ringer-solution.² After administration of pilocarpine the effect obtained from blood was increased ten-fold. 5. The effect in dilating the pupil in the excised frog eye.³ Tests 4 and 5 are less delicate and less specific than the others.

It is somewhat doubtful how far these tests can be utilised for detecting the presence and determining the amount of adrenaline in blood. Such reaction



FIG. 82.—Estimation of the relative amount of adrenaline in different extracts by comparing the effect of the same quantity of each upon the blood-pressure of a pithed cat. (T. R. Elliott.) The blood-pressure scale in mm. Hg is shown on the left.

1, 2, etc., represent the effect of successive doses containing 0.1, 0.2, etc., milligrams adrenaline chloride. At 4 a double tracing is noticeable; this amount having been repeated after 8.

either with blood or with serum is not necessarily due to adrenaline; some of the effects will occur after any adrenaline present has been destroyed by the passage of oxygen through the fluid.⁴ Moreover, blood generally contains a substance which actively stimulates plain muscle of the intestine⁵ (see fig. 30, p. 54), and this masks the inhibitory effect of adrenaline upon this tissue. Nevertheless the autacoid is under some circumstances passed into the blood in sufficient amount to be rendered evident by most of the above tests.

G. N. Stewart was unable to detect the presence of adrenaline in the general

¹ Oliver and Schafer, *op. cit.* Laewen, *Arch. f. exper. Path. u. Pharm.*, li., 1904. An exact method of employing this test is described by Trendelenburg, *ibid.*, lxi., 1910.

² *Journ. Physiol.*, xlv., 1912.

³ S. J. Meltzer and Auer, *op. cit.*, 1904; Ehrmann, *op. cit.*, 1905; W. H. Schultz, *Journ. Path. Exper. Therap.*, i., 1909. R. G. Hoskins uses the excised iris (*Journ. Pharm. and Exper. Therap.*, iii, 1911) and records effects in dilutions of from 1 in 10 millions to 1 in 100 millions.

⁴ Falta and Fleming, *Munch. med. Wochenschr.*, l., 1911.

⁵ G. N. Stewart, *Journ. Exper. Med.*, xiv., xvii., 1911 to 1913; J. M. O'Connor, *Arch. f. exper. Path. u. Pharm.*, lxxvii., 1912; E. Sharpey-Schafer, *Quart. Journ. Exper. Physiol.*, xiii., 1923.

blood-stream. O'Connor, who states that plasma, not serum, must be employed in testing for adrenaline in blood, since the substance which is antagonistic to it (see previous page) is formed in the process of coagulation,¹ found it easy to show the presence of adrenaline in the suprarenal veins (rabbit) but not in the ordinary blood taken from peripheral arteries or veins. The amount is in any case normally very small, even in the suprarenal vein; not more than about two parts in a million, according to R. G. Hoskins and M'Clure;² and sometimes much less. Stewart and Rogoff found the average output in 94 cats³ 0.000225 mg. per kilo. per minute: the concentration from 1:800,000 to 1:14,000,000—the nature of the anæsthetic had something to do with this. Taking the rate of blood-flow into consideration, they came to the conclusion that the output was fairly steady, being slightly more in the female than in the male. The amounts obtained in the dog and monkey (per kilo. and per minute) were nearly the same as those in the cat.

The rate of passage into the blood is certainly slow under normal conditions. If only a very small percentage is present, the blood-pressure would be lowered by it instead of raised; we cannot, therefore, assume that the normal tone of the vascular system depends on the presence of adrenaline in the blood, although, that the maintenance of vascular tone is in some animals assisted in this manner is shown by the result of compressing the suprarenal vein. Such compression may be followed by a gradual fall of blood-pressure, which quickly recovers, and, indeed, more than recovers its former height on relieving the compression.⁴ It is possible that the partially resumed tone of peripheral vessels which comes on after section of their nerves may be due to a compensatory increase of adrenaline in the blood, perhaps assisted by the circumstance that after section of its nerves plain muscular tissue becomes more sensitive to the influence of adrenaline.

E. A. Park, working with Janeway, states that although he could get inhibition of the tone of a strip of coronary artery of the ox with a solution of adrenaline of 1 to 50 millions, and inhibition of bronchial musculature with a solution of 1 in 20 millions, he was unable to prove the presence of adrenaline in circulating

¹ This is also affirmed by C. Heymans for portal blood (*Journ. de physiol.*, xix., 1921). But G. N. Stewart (*Journ. Exper. Med.*, xiv., 1911, xv. and xvi., 1912), W. H. Schultz (*ibid.*, xvi. and xvii., 1912 and 1913), and E. Ponder (*Quart. Journ. Exper. Physiol.*, xiii., 1923) obtained the same results with uncoagulated as with coagulated blood. Ponder finds that the material is present in the red corpuscles as well as in the plasma or serum.

² *Amer. J. Physiol.*, xxxi., 1912.

³ *Ibid.*, lxvi., 1923.

⁴ Strehl and Weiss, *Arch. f. d. ges. Physiol.*, lxxxvi., 1901; Burton-Opitz and Edwards, *Amer. Journ. Physiol.*, xli., 1916. Young and Lehmann (*Journ. Physiol.*, xxxvii., 1908) and Hoskins and M'Clure (*Amer. Journ. Physiol.*, xxx., 1912) got no fall from ligaturing the suprarenal veins. According to Gley and Quinquaud, the results are not constant (*C. r. soc. biol.*, lxxxii., 1919). They contend that under normal circumstances the cutting off of the supply of adrenaline to the general circulation is without result. But other effects on the circulation (heart) have been noted, which make it fairly certain that the regular secretion of adrenaline into the blood—although very small in amount—may produce physiological changes.

blood, although a positive result was got with blood from the suprarenal vein.¹ In the carotid blood of the rabbit, Trendelenburg² estimated the amount of adrenaline, as tested by the frog-perfusion method, to be not more than 1 part to 1 or 2 billions, an amount which would have no obvious effect on mammalian organs. Trendelenburg also estimated the amount of adrenaline in the blood of the suprarenal vein of a cat, and found that on the average 0.003 mg. was passed out of the two organs per minute, the concentration being not more than 1 part to a milliard, which is far too small to affect blood-pressure or to be detected by a slip of intestinal muscle. From the data thus obtained, he reckons that about 5 mg. per kilo. body-weight is formed in twenty-four hours. After draining off a large quantity of blood, and thus causing a considerable fall of blood-pressure, although, in consequence of the lessened flow of blood, the absolute amount of adrenaline passed per minute was not increased, the relative amount was greater than normal.³ Looking at the smallness of the figures in Trendelenburg's determinations, one is disposed to doubt whether the effects obtained by the frog-perfusion method from blood are wholly due to adrenaline. Borberg⁴ was never able to obtain dilatation of the pupil of the excised frog eye with blood either normal or pathological, although this is a fairly delicate test for adrenaline.

Despite many assertions to the contrary, there appears to be little doubt that discharge of adrenaline may under some circumstances occur from the suprarenals in sufficient amount to produce some of the symptoms caused by intravenous injection of the autacoid. Nevertheless such secretion is not indispensable for life, since none occurs after excision of one suprarenal and section of all the nerves passing to the other.⁵ This can be shown not only for the cat, in which the subject has been principally worked out, but also for the dog and monkey.⁶

W. Cramer⁷ finds that β -tetrahydronaphthylamine causes not only an outpouring of adrenaline into the blood, but also the formation of fresh adrenaline in the cells of the medulla. Cramer also states, in confirmation of Bedford and Jackson,⁸ that post-operative shock is followed by increase of secretion, the medullary cells remaining fully charged. Increased secretion also occurs immediately after a severe hæmorrhage, but in this case the cells become depleted and only gradually refill with secreting granules.

¹ *Journ. Exper. Med.*, xvi., 1912.

² *Arch. f. exper. Path. u. Pharm.*, lxiii., 1910 ; lxxix., 1915.

³ *Zeitschr. f. Biol.*, lvii., 1911. See also on the effect of hæmorrhage, W. Cramer, below.

⁴ *Skand. Arch. f. Physiol.*, xxvii., 1912.

⁵ Nor after destruction of the medulla of one suprarenal and removal of the whole of the remaining organ; neither of these operations produces any adverse symptoms.

⁶ Stewart and Rogoff, *Journ. Pharm. and Exper. Therap.*, xiii., 1919; *Amer. Journ. Physiol.*, xlviii., 1919. See on the question of the amount of adrenaline in the blood in physiological conditions G. N. Stewart, in *Endocrinology*, v., 1921, where most of the literature of the subject will be found.

⁷ *Proc. Physiol. Soc.*, in *Journ. Physiol.*, lii., 1918.

⁸ *Proc. Soc. Exper. Biol.*, xiii., 1916; and *Amer. Journ. Physiol.*, xliii., 1917.

CHAPTER XX

THE SUPRARENAL CAPSULES (*continued*)

INFLUENCE OF THE NERVOUS SYSTEM ON THE SECRETION

IT was shown by A. Biedl¹ that stimulation of the splanchnic nerves is accompanied by increased blood-flow through the organ. The result is even better marked when these nerves have been cut and allowed to degenerate for two or three days so that only vasodilators are acting.² Tscherboksaroff,³ in confirmation of an observation by G. P. Dreyer,⁴ found that during excitation of the splanchnic in a dog the blood passing from the suprarenal capsule by its vein produces a greater effect in raising the blood-pressure of another dog than the blood of the suprarenal vein under ordinary circumstances, and concluded that adrenaline is passed into the traversing blood under the influence of impulses conveyed by this nerve. He also found a larger amount of adrenaline in the suprarenal capsule as the result of such stimulation. Section of the splanchnic caused a diminution of adrenaline in the gland and in the blood flowing from it. He found no effect from stimulation of the vagus, and none from atropine or pilocarpine,⁵ but got an increase with physostigmine.⁶

But the actual proof of secretion under the influence of nerves seemed most satisfactorily furnished by the experiment of Asher,⁷ who found that after ablation of the stomach, intestines, and all the other abdominal organs, except the liver, in order to eliminate the direct effect which would be obtained on their blood-vessels, stimulation of the splanchnics still causes a marked rise of blood-pressure which fails if the suprarenal veins are compressed.⁸

Elliott and Tuckett⁹ were not able to exhaust the suprarenal of its adrenaline by stimulation of its nerves.

Section of the splanchnics diminishes the amount of adrenaline which is

¹ *Arch. f. d. ges. Physiol.*, lxvii., 1897.

² Hallion got only constriction of the suprarenal vessels in the normal animal (*C. r. soc. biol.*, lxxxiv., lxxxv., 1921).

³ *Arch. f. d. ges. Physiol.*, cxxxvii., 1910. See also Burton-Opitz and Edwards, *Amer. Journ. Physiol.*, xliii., 1917.

⁴ *Amer. Journ. Physiol.*, ii., 1899.

⁵ Confirmation of R. Ehrmann, *Arch. f. exper. Path. u. Pharm.*, lv., 1906.

⁶ Stewart and Rogoff in an extensive series of researches on the action of drugs (*Journ. Pharm. and Exper. Therap.*, vols. xiii., xiv., xvi., and xvii., 1919 to 1921) got for the most part similar results. Dale and Laidlaw (*Journ. Physiol.*, xlv., 1912) found, however, a distinct increase with pilocarpine.

⁷ *Zentrbl. f. Physiol.*, xxiv., 1910; *Zeitschr. f. Biol.*, lviii., 1912.

⁸ See, however, the criticism of D. Cow, p. 139.

⁹ *Journ. Physiol.*, xxxiv., 1906.

passed into the blood : but, according to Elliott,¹ it is only the reflex secretion which is affected ; an automatic secretion goes on all the time. Stewart and Rogoff state, however, that secretion ceases on cutting these nerves,² and Pende³ found that section of the splanchnics leads eventually to atrophy of the medulla.

Elliott came to the conclusion that morphine, chloroform, ether, etc., all of which cause expulsion of adrenaline from the suprarenal capsules, act through the splanchnics. He further found that after section of the nerves to one capsule, the amount of adrenaline in this gland was almost exactly the same as in its untouched fellow.

Stewart and Rogoff confirm Elliott's observation that in cats, which are excited by that drug, morphine produces discharge and exhaustion of the suprarenals, and that if the splanchnics on one side are cut the gland of that side remains unaffected. They find that strychnine has a similar effect. On the other hand they deny that asphyxia causes increase of secretion, although it produces hyperglycæmia and glycosuria. The influence of the spinal cord is shown by the fact that section of the cord in the cervical region has no effect on the output of adrenaline as produced by dogs, whereas if the section is between the 4th and 5th thoracic segments the secretion is checked, and semi-section checks it on the same side as the lesion. Direct stimulation of the cut cord causes discharge of adrenaline. In animals (cats) in which all the nerves to the suprarenals were cut, no adrenaline could be detected in the blood of the suprarenal vein fifteen weeks after operating, and the animals showed no adverse symptoms.⁴

A number of other drugs, such as nicotine, strophanthus, and camphor, also cause a discharge of adrenaline, which fails if the splanchnics are cut or the cord severed.⁵

Dale and Laidlaw⁶ found that whilst nicotine and pilocarpine stimulate the uterine muscle of the non-pregnant cat when it is isolated, they have an inhibitory effect upon it if they are injected into the living animal. They ascribe this inhibition to the production of increased secretion of adrenaline by the suprarenals under the stimulation of these drugs.

After removal of the superior cervical ganglion and consequent sensitivation of the fibres of the dilatator pupillæ, the excess of adrenaline which is secreted on stimulation of the splanchnics is easily rendered evident by its effect upon the pupil.⁷

Cannon and Rapport,⁸ using the denervated heart as indicator, obtained an

¹ *Journ. Physiol.*, xlv., 1912.

² *Proc. Soc. Exper. Biol.*, xiii., 1916.

³ *Policlinico*, 1903.

⁴ The subject is reviewed at length by J. M. Rogoff in the *Journ. of Lab. and Clin. Med.*, iii., 1918.

⁵ Cannon, Aub, and Binger, *ibid.*, iii., 1912 ; Richards and Wood, *Journ. Pharm. and Exper. Therap.*, vi., 1915 ; Asher and Schneider, *Biochem. Zeitschr.*, cxxxiii., 1922.

⁶ *Journ. Physiol.*, xlv., 1912.

⁷ Joseph and Meltzer, *Proc. Amer. Physiol. Soc.*, in *Amer. Journ. Physiol.*, xxix., 1912. See also Elliott, *op. cit.* The latent period of the reaction is the same as when adrenaline is injected into a vein. It is not obtained if the blood from the suprarenal veins is prevented from reaching the general circulation. Stewart, Rogoff, and Gibson, *Journ. Pharm. and Exper. Therap.*, viii., 1916 ; also Stewart and Rogoff, *ibid.*

⁸ *Amer. Journ. Physiol.*, lviii., 1921. See also Cannon and Uridil, *ibid.*

increased rate of beat of twenty-nine per minute on stimulating the splanchnics ; this was reduced to six per minute after removing the suprarenals ; and this small increase disappeared when the hepatic nerves were cut ; from which they infer that a pulse-accelerating autacoid is also furnished by the liver, an inference confirmed by stimulation of the hepatic nerves. They obtained a slowing of the rate on removing the suprarenals (without stimulation), and found that to bring the rate again to normal it was necessary to inject adrenaline intravenously in an amount equal to 0.0007 mg. per kilo. per minute. They calculate that the normal output of the two suprarenals is about 0.0035 mg. per kilo. per minute, which is more than ten times the amount given by Stewart and Rogoff (p. 154). They also state that stimulation of the central end of the cut vagus or of the depressor slows the denervated heart, and explain this result by supposing it to be a reflex effect inhibiting the secretion of adrenaline. The effect disappears on section of the brain stem just below the corpora quadrigemina, and is not seen if the suprarenals are removed. Further, Tournade and Chabrol¹ have shown, using a dog (A) from which both suprarenals had been removed and the blood-pressure had fallen considerably, that on connecting the jugular of A to a lumbo-capsular vein of another dog (B), from which one suprarenal had been removed, the blood-pressure in A rose considerably, but fell in both dogs on cutting the opposite splanchnic of B. On now stimulating this splanchnic of B a rise of blood-pressure was caused, both in B itself, and a little later also in A. This appears to be a crucial experiment to demonstrate the outpouring of adrenaline into the blood as the result of nerve stimulation in quantity sufficient to cause by itself a definite rise in blood-pressure. But Gley and Quinquaud find that the effect can be obtained even if both suprarenals are removed from the animal the splanchnics of which are stimulated.² It is conceivable, however, that accessory glands may yield enough adrenaline to produce the effect.

The inhibition of the intestine which is caused by splanchnic stimulation is not dependent on outpouring of adrenaline secretion from the suprarenal capsules, for it will occur after ablation of these organs.³

There appears to be a reflex centre for the secretion of adrenaline in the floor of the fourth ventricle,⁴ subject to both excitatory and inhibitory influences reaching it through afferent nerves,⁵ or coming from the higher nerve centres in the brain.

¹ *C. r. soc. de biol.*, lxxxv., 1921, and lxxxvi., 1922. See also Tournade, *Journ. de méd. et de chir. de l'Afrique du Nord*, 1922. Zunz and Govaerts (*C. r. soc. biol.*, lxxxvii., 1922, and *C. r. soc. belg. de biol.*, i., 1923), in repeating these experiments, were sometimes unable to obtain pressor effects in the second dog of a cross-circulation experiment in which the splanchnics of the donor were stimulated, although 1 mg. of adrenaline introduced into the blood of the donor produced a marked rise of pressure in the receiver: only when the cross-circulation was very free did they obtain a positive result.

² *C. r. soc. biol.*, lxxxviii., 1923.

³ Wertheimer and Duvillier, *C. r. soc. biol.*, lxxxv., 1921.

⁴ It is interesting to note that Bernard's *piqure* increases the rate of the denervated heart even if the hepatic nerves are divided, but not if the suprarenal veins are clamped (Corrasco-Formiguera, *Amer. Journ. Physiol.*, lx., 1922).

⁵ For various ways in which a reflex discharge of adrenaline may be brought about, see F. A. Hartman, *Amer. Jour. Physiol.*, lxiii., 1923 ; Hartman, McCordock, and Loder, *ibid.*, lxiv., 1923.

In the cat Cannon and de la Paz¹ found that the dilatation of the pupils and upstanding of the fur which accompany sudden alarm or excitement are associated with an increased outpouring of adrenaline into the suprarenal veins, and draw attention to the fact that many of the phenomena which characterise violent emotional states (both in animals and man) are similar to those which are produced by excess of the suprarenal autacoid in the blood. To this excess thus produced Cannon applies the term "emergency secretion."

Cannon² contends that fear, rage, pain, and asphyxia all increase the amount of adrenaline poured into the blood, and indirectly increase its sugar content. These changes are beneficial under the circumstances; for the excess of adrenaline tends to lessen the movements of the alimentary canal, causes more blood to pass to the muscles, supplies more fuel for their energy, and increases the alertness of the nervous system. Stewart and Rogoff³ deny that these results are due to increased output of adrenaline. They state that they may be obtained after the suprarenal capsules have been extirpated or their veins tied: and although admitting that the secretion is dependent on the nervous system, they refuse to admit that it is influenced by emotions.⁴

Nervous excitement causes contraction of the melanophores of the horned toad (*Phrynosoma*) even in an area of skin of which the nervous connexion is severed. But this does not occur if the circulation in the area is arrested or if the suprarenals are extirpated.⁵

On the whole the evidence is in favour of the view that there is not only a normal and fairly constant passage of adrenaline into the blood, but that this secretion is under the influence of the nervous system through the splanchnics. Although usually insufficient to produce any externally appreciable action, it may be temporarily increased under conditions of nervous excitation, whether caused by drugs (especially strychnine), by emotions, or by reflex stimulation, and may then produce definite reactions, similar to those obtainable by intravenous injection of the autacoid.⁶

Cannon and Hoskins⁷ and G. Anrep,⁸ showed that although a denervated limb or organ exhibits constriction of its blood-vessels on stimulating an afferent nerve, this fails and is replaced by dilatation if the suprarenals have been

¹ *Amer. Journ. Physiol.*, xxviii., 1911. They used the intestinal slip method for determining the relative amount of adrenaline, but in other experiments Cannon has employed the denervated heart of the animal under experiment as a test object to determine the presence of an excess of adrenaline.

² *Amer. Journ. Psych.*, xxv., 1914; *Amer. Journ. Physiol.*, xxxiii., 1914.

³ *Amer. Journ. Physiol.*, lii., 1920.

⁴ The subject is discussed at length in *Endocrinology and Metabolism*, ii., 1922, in special articles by G. N. Stewart and W. B. Cannon respectively.

⁵ A. C. Redfield, *Journ. Exper. Zool.*, xxvi., 1918.

⁶ S. Kadama (*Tohuko Journ. Exper. Med.*, iv., 1923) got an increased rate of secretion on stimulating a sensory nerve (using the method of Stewart and Rogoff). F. A. and W. B. Hartman (*Amer. Journ. Physiol.*, lxxv., 1923) find that external cold causes increased secretion in cats (denervated iris as indicator).

⁷ *Amer. Journ. Physiol.*, xxix., 1911.

⁸ *Journ. Physiol.*, xlv., 1912. See also Pearlman and Vincent, *Endocrinology*, iii., 1919.

extirpated. Stewart and Rogoff, on the other hand, find no difference whether the suprarenals are intact or removed.¹

Florovsky,² who got secretion from a denervated salivary gland on stimulating sensory nerves, found that this reflex secretion did not occur if the suprarenals were extirpated. Cardiac acceleration also obtained under like circumstances.³ Cannon and Mendenhall⁴ have further shown that the blood of an animal which has been subjected to nervous excitement clots more quickly than under normal circumstances; they state that this acceleration of coagulation is due to increase of adrenaline.

Anrep got a vasoconstrictor effect in a denervated limb from asphyxia, and Gley and Quinquaud found an increased amount of adrenaline in the blood of the suprarenal vein as a result of the same condition.⁵ But they

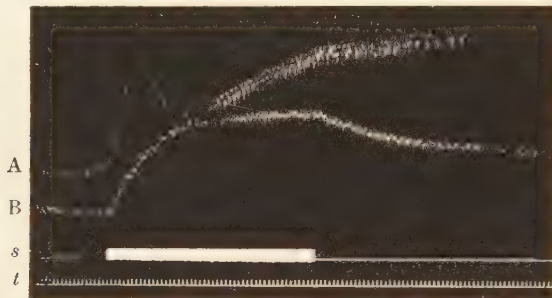


FIG. 83.—Effects on blood-pressure of stimulating the splanchnics in cat before (A) and after (B) removal of suprarenal capsules. (T. R. Elliott.

A, immediate rise, with dip, followed by a prolonged rise; B, immediate and prolonged rise, without dip; s, signal; t, time, in seconds.

consider that the rise of blood-pressure in asphyxia is not determined by the increased secretion of adrenaline, for they found no difference in the amount of such rise whether the suprarenals were extirpated or intact.⁶

Elliott found that in the cat the typical blood-pressure curve on stimulating the splanchnics is—(1) a rapid rise for about ten seconds; (2) a very distinct fall; followed by (3) a slow rise to or above the level of (1), continuing as long as the stimulus is applied (fig. 83).⁷ The first phase is obviously due to direct action of the splanchnics on the abdominal vessels, the second was regarded by Elliott as caused by the outpouring of adrenaline from the suprarenal capsules (effect of minimal dose), the third as the combined effect of a larger amount of adrenaline plus direct nerve action. The second phase fails if the

¹ *Amer. Journ. Physiol.*, lxxiii., 1923.

² *Bull. de l'Acad. d. sci. Petrograd*, ix., 1917.

³ Gasser and Meek, *Amer. Journ. Physiol.*, xxxiv., 1914; W. B. Cannon, *ibid.*, l., 1919.

⁴ *Ibid.*, xxxiv., 1914.

⁵ *Journ. de physiol.*, xvii., 1918.

⁶ *Arch. internat. de physiol.*, xviii., 1921.

⁷ *Journ. Physiol.*, xlv., 1912. This confirms an old observation by Johansson (*Arch. f. Physiol.*, 1891). Cf. also Lehndorff, *ibid.*, 1908.

suprarenals are tied off, and the third is modified and only shows a rise due to direct action of the nerves on the vessels.

Anrep¹ described stimulation of the splanchnics (in the dog) as producing a double rise of blood-pressure; he regarded the first rise as due to direct stimulation of the vasomotors, the second to the outpouring of adrenaline into the blood. The second rise is accompanied by acceleration of the denervated heart and constriction of denervated blood-vessels of the limbs.

Vincent and Pearlman's² experiments are confirmatory of those of Elliott. Their tracings show first a rapid rise in blood-pressure on stimulating the splanchnic, which rise may be marked by a slight "hump." The rise is followed by a considerable "dip," after which the pressure again rises to the level of the apex of the first rise, or somewhat higher, and is there main-

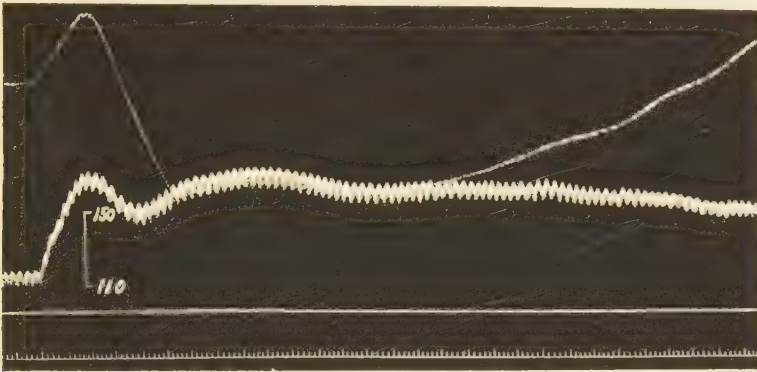


FIG. 84.—Dog: ether, morphia, curari; vagi cut.

Upper curve, volume of denervated hind-limb; lower curve, blood-pressure: time in secs. The right splanchnic was cut in the thorax and the peripheral end stimulated. (Figs. 84 and 85 are from Swale Vincent, "The Ductless Glands.")

tained during the stimulation. If the suprarenals are excluded from the circulation the hump and dip both disappear. If at the same time the volume of a denervated limb is recorded, there is in the first case an increase of volume due to passive expansion from the heightened blood-pressure; this is followed by a prolonged decrease of volume due to contraction of the cutaneous blood-vessels caused by the secreted adrenaline. But if one of the splanchnics is stimulated after clamping the suprarenal veins on both sides, only the rise in blood-pressure caused by direct action on the vasoconstrictor nerves of the abdominal viscera is seen, and the limb only shows a passive increase in volume (*cf.* figs. 84 and 85). Similar effects are got reflexly from stimulation of the central end of one of the sciatic nerves.

¹ *Op. cit.*, 1912. See also Burton-Opitz and Edwards, *Amer. Journ. Physiol.*, xli., 1916, and B. A. Houssay, *C. r. soc. biol.*, lxxxiii., 1920.

² *Trans. Roy. Soc. Canada*, 1917. See also Vincent in "The Ductless Glands," 1922. Similar results have been obtained by Houssay and Mareoni (*C. r. soc. biol.*, lxxxvii., 1922) in dogs in which the circulation was cut off from all the abdominal viscera except the suprarenals.

Gley and Quinquaud,¹ on the other hand, find that the double rise of blood-pressure, described as a result of splanchnic stimulation, is not a constant phenomenon, and that when it occurs it is not altered by removal of the suprarenals (fig. 86). They state that it fails to show itself in 25 per cent. of normal dogs and in a larger proportion of cats, and that it is rarely seen in the rabbit. Since it may show itself in completely decapsulated dogs, they contend that the

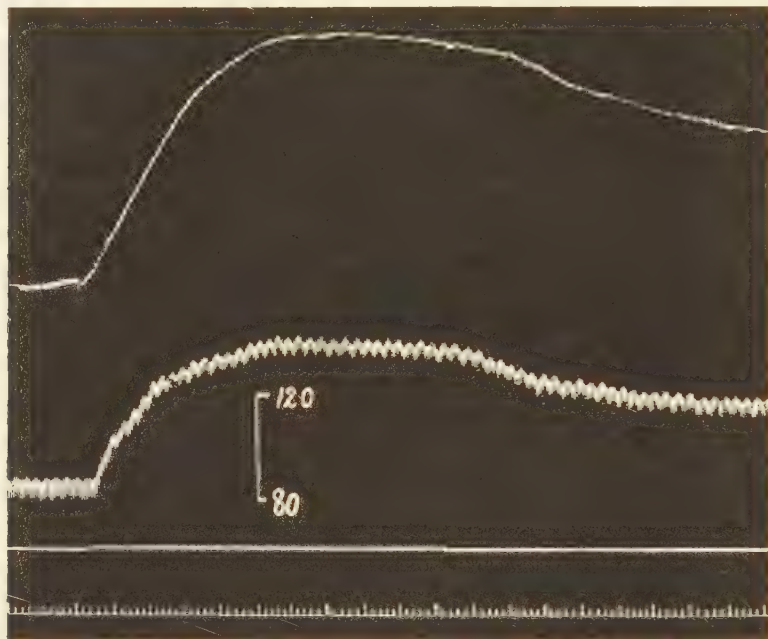


FIG. 85.—Effect of stimulating the right splanchnic in the same dog after clamping both suprarenal veins.

The dip in the blood-pressure curve and the diminution in volume of the hind-limb are no longer seen.

secretion of adrenaline cannot be the cause of the dip or after-rise: these must be due, as Lehdorff suggested, to nervous influences.

It will be seen that the evidence regarding the effects of splanchnic stimulation before and after decapsulation is discrepant, and the reason for the discrepancy is not very apparent. Seeing, however, that even the same observers occasionally get different results in different animals, the explanation is probably to be found in some idiosyncrasy in the animals employed. If these possess many accessory suprarenals there might be a sufficient amount of adrenaline poured out into the blood even if the suprarenal veins are clamped or the suprarenals removed. In any case the subject is still obscure and requires further experiment for its elucidation.

¹ *Journ. de physiol.*, xix., 1921. See also Stewart and Rogoff, *Proc. Soc. Exper. Biol.*, xx., 1922.

Bernard's sugar puncture of the medulla oblongata, which causes hyperglycæmia and glycosuria by mobilisation of the liver glycogen and its discharge as glucose into the blood, is in considerable measure due to a greatly increased secretion of adrenaline from the suprarenal medulla, which is stimulated through the splanchnic nerves. If the suprarenals are extirpated or their

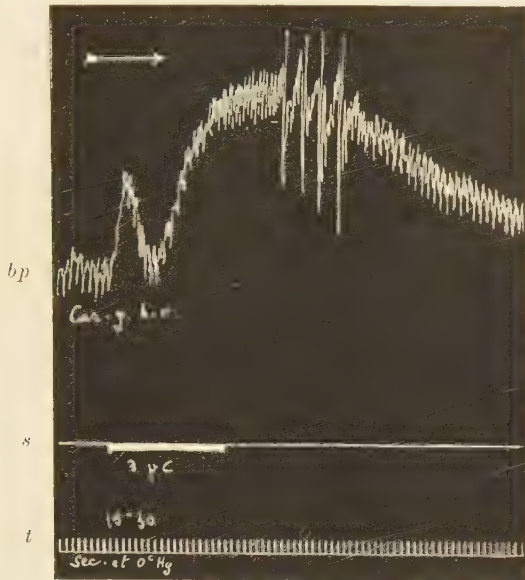


FIG. 86.—Tracing showing double rise of blood-pressure from stimulation of splanchnic in dog from which both suprarenals had been removed. (Gley and Quinquaud.)

bp, blood-pressure (carotid); *s*, signal; *t*, time, in seconds, and zero of Hg manometer.

veins clamped the effect of the sugar puncture is greatly lessened, although there may be some direct effect obtained by the action of the hepatic nerves upon the liver cells. The sugar puncture causes profound changes in the suprarenal medulla; its cells become vacuolated and discharge their granules, and its adrenaline content is greatly diminished.¹

¹ R. H. Kahn, *Arch. f. d. ges. Physiol.*, cxl., 1911, and cxlvi., 1912. Kahn was unable, however, to find adrenaline in the rabbit's blood after Bernard's *piqûre*. *Ibid.*, cxliv., 1912.

CHAPTER XXI

THE SUPRARENAL CAPSULES (*continued*)

THE EMPLOYMENT OF SUPRARENAL EXTRACTS AND OF ADRENALINE IN SURGERY AND MEDICINE ¹

IN the administration of adrenaline it must be borne in mind that alkalies, oxidising agents (such as chlorine and iodine, and nitric and chromic acids), all easily dissociated salts, salts of iron and of the heavy metals, and particularly formaldehyde, are incompatible, and must be avoided.²

In surgery the chief use of adrenaline is as a styptic. Applied to the oozing surface of wounds it arrests hæmorrhage by constricting the small arteries, but its vasoconstrictor action is insufficient to close larger vessels, although the bleeding from these may be diminished. It is valuable in epistaxis and hæmatemesis. It is largely used in operations on the eye and on the teeth. It is then given in conjunction with a local anæsthetic, such as cocaine, eucaïne, or novocaine. It blanches the mucous membrane to which it is applied (conjunctiva) or into which it is injected (gums), and by diminishing the rate of absorption of the analgesic with which it is combined prolongs the action of the latter. Many superficial operations can be performed by injecting such combinations into and under the skin of the part to be operated upon. It is also used combined with eucaïne, etc., in the production of spinal anæsthesia: the proportion of adrenaline need not be more than 1:20,000. In general anæsthesia—especially in chloroform anæsthesia—it is indicated in cases of heart failure, although if the heart is completely paralysed by the anæsthetic it is not readily revived by adrenaline.³ To produce an immediate action upon the heart it may be injected directly into the cardiac musculature through the chest wall.⁴

In medicine, adrenaline is of use in the treatment of bronchial asthma, on account of its inhibitory action on the bronchial musculature. For this purpose it can be given by the mouth, but administered in this way it is less efficacious and requires much larger doses than given subcutaneously or intramuscularly. It may also be administered by inhalation in the form of a fine spray: a

¹ See on this subject H. Boruttan in *Handb. d. Serumtherapie*, 1910. Attention was early directed to the therapeutic uses of suprarenal extracts by W. H. Bates. *Medical Record*, 1898.

² The therapeutic relations and chemical reactions of adrenaline are dealt with in *The Prescriber*, xvii., May 1923.

³ Schafer and Scharlieb, *Trans. Roy. Soc. Edin.*, xli., 1904.

⁴ C. Walker, *Brit. Med. Journ.*, i., 1921, p. 46; E. Vogt, *Münch. med. Wochenschr.*, 1921, p. 732.

very dilute solution should prove sufficient. Opinions differ as to its use in internal hæmorrhage, especially pulmonary hæmorrhage. It has been thought to be dangerous in such cases on account of its pressor action, but this is largely due to its causing constriction of the arterioles, both systemic and pulmonary. Administered subcutaneously, or by the mouth, it has no perceptible pressor effect, but it is possible that an injured vessel will react with it more readily than an uninjured one. It must also be borne in mind that it increases the coagulability of the blood, and this will assist its action as an internal styptic. It appears to be of value in restraining serous effusions such as occur in the tunica vaginalis, the peritoneum, and the pleura. It has been administered by the mouth in cases of poisoning on account of the delay in absorption which occurs by reason of its vasoconstrictive action. It has also been recommended in surgical shock, but is inferior to pituitrin in combating this condition. It has been employed in cases of anaphylactic shock.¹ It is given by the mouth in diphtheria, especially when cardiac failure is threatening.² It has also proved beneficial administered subcutaneously in cases of heart block.³ Its employment in Addison's disease has been already referred to, and the effect of adrenaline in helping to overcome fatigue in this and other affections in which there is considerable muscular weakness must not be overlooked. As Vincent has pointed out, it would probably be best to give the whole gland in Addison's disease rather than adrenaline alone, since it seems undoubted that many of the symptoms are due at least as much if not more to cortical than to medullary deficiency. Adrenaline has been recommended in the treatment of osteomalacia.⁴ It has been employed successfully by local application to rodent ulcer, in which it probably acts as a styptic.⁵ Carnot and Slavu⁶ state, as the result of experiments on animals, that the process of osseous repair is markedly accelerated by the subcutaneous injection of small doses of adrenaline. It has been found beneficial in the treatment of tobacco amblyopia.⁷

Fröhlich and Loewi⁸ find that quite small doses of cocaine greatly increase the action of adrenaline both in intensity and duration. Most of the effects of adrenaline are also increased by pituitrin, and *vice versa*.⁹

¹ C. Parhon and G. Bazgan, *C. r. soc. biol.*, lxxix., 1916.

² H. D. Rolleston, *Brit. Med. Journ.*, 1907.

³ A. G. Phear and J. Parkinson, *Lancet*, i., 1922, p. 933.

⁴ Guthrie, *The Prescriber*, Nov. 1909; L. Bernard, *Presse méd.*, Nov. 1909.

⁵ Allan, *The Prescriber*, Dec. 1912.

⁶ *C. r. soc. biol.*, lxxviii., 1910.

⁷ P. A. Harry, *The Prescriber*, xvii., 1923.

⁸ *Arch. f. exper. Path. u. Pharm.*, lxii., 1910.

⁹ L. Kepinow, *ibid.*, lxxvii., 1912; B. A. Houssay, *Wien. klin. Woch.*, 1913; D. Cow, *Journ. Physiol.*, lii., 1919.

CHAPTER XXII

THE SUPRARENAL CAPSULES (*continued*)

RELATIONS OF THE SUPRARENALS WITH OTHER ENDOCRINE ORGANS AND SECRETING GLANDS

VARIOUS organ extracts, viz. liver, kidney, thyroid, parathyroid, pituitary, thymus, pancreas, testicle, and ovary are stated to produce an increased secretion of adrenaline into the blood,¹ and thyroid extract has been described as augmenting the physiological effects of adrenaline. But this is doubtful (see pp. 43, 44), and is certainly not specific: for extracts of some other organs, and particularly of liver, were found by Gley and Quinquaud to have more effect than thyroid.²

Gley also finds that thyroid removal does not diminish the activity of adrenaline given intravenously.

J. B. Collip³ states that tissue extracts not only augment the effect of adrenaline upon blood-pressure, but are capable of converting the fall which results from minute doses of adrenaline into a rise. He further finds that most of these extracts (heart, spleen, pancreas, testis, both lobes of pituitary, thyroid, and thymus) stimulate the uterus of the rat, guinea-pig, and non-pregnant dog and cat, and antagonise the inhibitory effects of adrenaline. According to Pugliese,⁴ extracts which depress blood-pressure—and this is the case with most—are antagonistic to the action of adrenaline upon the vascular system.

Indirectly, the secretion of the suprarenal medulla undoubtedly exerts an influence upon many diverse organs and glands—including most of the other ductless glands: this is due to the fact that adrenaline activates sympathetic nerve-endings throughout the body.

With the Sexual Glands.—A direct relationship between the development of the sexual glands and that of the suprarenals may be regarded as probable, although the nature of the relationship—whether through the nervous system or, as is more likely, through chemical agencies—is not precisely known. The connexion appears to be more with the cortex of the adrenals than with the medulla (see p. 105). During pregnancy the whole gland under-

¹ Ott and Scott, *Journ. Pharm. and Exper. Therap.*, iii., 1912.

² Gley and Quinquaud, *Arch. internat. de physiol.*, xiv., 1913. They used pieces of rabbit intestine as indicator.

³ *Amer. Jour. Physiol.*, liii., 1920.

⁴ *Biochem. e terap. sper.*, viii., 1921.

goes enlargement: the cortex much more than the medulla.¹ Whilst hypertrophy of the cortex is stated to occur as the result of castration, various observers have found that enlargement is also associated with sexual precocity. Further, in diseased conditions resulting in hypoplasia of the adrenals, changes in the testicles, especially in their interstitial cells, have been noted.

Elliott and Tuckett do not admit any special connexion between the suprarenals and the sexual glands. They associate the cortex more particularly with the development of the muscular system. They also point out that the lower the animal in the vertebrate, or at any rate in the mammalian series, the greater is the relative development of the cortex.²

With the Liver.—The most noteworthy effect on this organ is upon its glycogenic function, for, as we have seen, the autacoid of suprarenal medulla, even in small doses, produces a rapid conversion of the liver glycogen into sugar, which passes into the blood and eventually into the urine (see pp. 149, 150). The effect is similar to that caused by Bernard's sugar puncture of the medulla oblongata and by excitation of the splanchnics. It will be remembered that after section of the splanchnics Bernard found that puncture of the medulla oblongata fails to cause glycosuria. The puncture probably produces excitation of cells in the nerve-centre. These give origin to impulses travelling along the splanchnics to the suprarenals, and thus cause the outpouring of an excess of adrenaline into the blood; this again excites the terminal apparatus of the sympathetic nerves in the liver-cells.

R. H. Kahn³ noticed that, after the sugar puncture, if one suprarenal is left its medulla shows increased secretion, and less adrenaline is stored in it than normally. This does not occur if the splanchnic on that side is cut. Similar observations have been made by Fujii.⁴ Kahn states that in the guinea-pig the blood can be shown to contain an excess of adrenaline after the sugar puncture. A. Mayer⁵ found that Bernard's puncture is not effective after removal of the suprarenals. On the other hand, Freund and Marchand⁶ state that although glycosuria is not seen under these conditions, hyperglycæmia is produced. A. Jarisch⁷ finds that the sugar puncture does not cause either hyperglycæmia or glycosuria if the nerves of the suprarenal are cut, whereas when the nerves to the liver are cut, and those to the suprarenal intact, the sugar puncture is effective. Trendelenburg and Fleischhauer⁸ contend that the amount of adrenaline produced after the sugar puncture is insufficient to account for the glycosuria, and that the effect must be a direct one on the liver through the splanchnics.

¹ In birds (pigeon) O. Riddle finds that the suprarenals increase in weight during ovulation (*Amer. Journ. Physiol.*, lxi., 1923).

² For the experimental and clinical evidence of the influence of the suprarenal bodies on the genital system, see Swale Vincent, *Trans. Amer. Gynec. Soc.*, 1917.

³ *Arch. f. d. ges. Physiol.*, cxi., 1911, cxliv. and cxlv., 1912.

⁴ *Tohoku Journ. Exper. Med.*, i., 1920. The history of the subject is given in this paper.

⁵ *C. r. soc. biol.*, lx., 1906.

⁶ *Arch. f. exper. Path. u. Pharm.*, lxxvi., 1914.

⁷ *Arch. f. d. ges. Physiol.*, clviii., 1914.

⁸ *Zeitschr. f. exper. Med.*, i., 1913.

Macleod and Pearce¹ observed that adrenaline produces hyperglycæmia even after division of the hepatic plexus (which is not the case with the hyperglycæmia caused by stimulation of the splanchnics), and that only when the suprarenals are intact is it possible to produce hyperglycæmia by stimulation of the nerves of the liver. Adrenaline is, therefore, in some way necessary to the action of these nerves. It is stated that the effect of adrenaline on the liver glycogen can be prevented by atropine.² Ergotoxine also antagonises this action of adrenaline (see p. 149).

If the liver is rendered free from glycogen, adrenaline injection will not only still produce hyperglycæmia and glycosuria, but may, even in fasting animals, cause glycogen to be stored; this is associated with the fact that the metabolism of proteins is increased under the influence of adrenaline, and the protein is in this case the source of the carbohydrate which is formed. On the other hand, O. Schwarz found the liver glycogen to disappear in rats in which the suprarenals had been removed, although it could be restored by liberal feeding with glucose and cane sugar (but not by levulose or starch). If the glycogen of the liver is got rid of by phloridzin, administration of adrenaline does not increase the glycosuria.³

That the effect of Bernard's *piqûre* is not entirely due to outpouring of adrenaline from the suprarenals is shown by the fact that in rabbits which have recovered completely from their total removal, and the livers of which are well stored with glycogen, the *piqûre* still causes hyperglycæmia.⁴ This may, however, well be due to the vicarious action of supplementary chromophil bodies. S. Kuriyama⁵ found ablation of the suprarenals to have no distinct effect on the glycogenic function of the liver.

With the Pancreas.—Pemberton and Sweet⁶ found removal of the suprarenals to cause a flow of pancreatic juice which is stopped by injection of adrenaline, although under normal conditions the flow of pancreatic juice seems not to be affected by the intravenous injection of adrenaline, at least in moderate doses.⁷ But it is the internal secretion which is mainly affected by this hormone. Herter and Wakeman⁸ found that the mere swabbing of the exposed pancreas with adrenaline solution provokes intense glycosuria, comparable with that produced by extirpation of the organ. The glycosuria and the hyperglycæmia caused by pancreatic extirpation are, however, increased, as several observers have found, by adrenaline; so that its effect on carbohydrate metabolism is not wholly exerted through the pancreas, but part must be directly on the liver.

¹ *Amer. Journ. Physiol.*, xxix., 1912. The effect of stimulating the splanchnics on the glycogenic function of the liver and the part played by the suprarenal capsules in causing the hyperglycæmia and glycosuria which result from such stimulation is dealt with by Macleod and his coadjutors in a series of papers in the same journal from 1907 to 1915. See also Doyon, Morel, and Kareff, *Journ. de physiol.*, vii., 1906.

² Doyon and Gautier, *C. r. soc. biol.*, lxiv., 1908.

³ A. J. Ringer, *Journ. Exper. Med.*, xii., 1910.

⁴ Stewart and Rogoff, *Amer. Journ. Physiol.*, xlvi., 1918. Wertheimer and Battez obtained a similar result in the cat (*C. r. soc. biol.*, lxxvi., 1914).

⁵ *Journ. Biol. Chem.*, xxxiv., 1918.

⁶ *Arch. intern. Med.*, i., 1908, and x., 1912.

⁷ See, however, Mann and M'Lachlin, *Journ. Pharm. and Exper. Therap.*, x., 1917.

⁸ *Virchow's Arch.*, clxix., 1902.

We have, in fact, already seen that adrenaline has a direct effect on the glycogen storage of the liver. But this again is influenced by the internal secretion of the pancreas. Thus Zuelzer¹ failed to get adrenaline glycosuria when he injected pancreas extract at the same time as the adrenaline, an effect doubtless due to "insulin," which was then unknown. On the other hand, he states that tying the suprarenal veins is effectual in preventing glycosuria pancreatopriva. These experiments indicate that carbohydrate metabolism is in some way regulated by the interaction of the suprarenals and pancreas. Adrenaline and pancreas extract have opposing effects on the amount of glucose in blood, the former increasing, the latter decreasing it.² Liver extract slightly decreases it.³ Graham Lusk,⁴ from a study of the respiratory quotient in glucose-fed dogs to which adrenaline was administered, came to the conclusion that this autacoid does not act on carbohydrate metabolism by specifically inhibiting the internal secretion of the pancreas. The subject will again come up for discussion when the internal secretion of the pancreas is dealt with.

According to G. M. Mackenzie,⁵ if a dog which has been rendered diabetic by removal of the pancreas has the suprarenals removed, there is a rapid disappearance of the excess of sugar from the blood.

But Houssay and Lewis obtained a contrary result in two dogs which survived the double operation a short time. In one of these, however—the one which showed most glycosuria—there was a small amount of the suprarenal medulla left.

With the Pituitary Body.—The mutual relations of the pituitary and suprarenals will be considered when the functions of the pituitary are dealt with.

*With the Thyroid.*⁶—E. Gley has investigated the effects of thyroid removal (dogs and rabbits) upon the reaction to adrenaline, and has found that the activity of this autacoid is not diminished by the operation.⁷ He had previously found that the administration of extract of thyroid has no specific influence upon the action of adrenaline.

Gley and Quinquaud find that small doses of thyroid have no effect upon the amount of adrenaline passed into the blood, although very large doses may augment it. Moreover, extracts of other organs, such as the liver, give similar results.⁸

According to Marine and Baumann,⁹ the cortex of the suprarenals exercises an inhibiting influence over the thyroid, while the medulla produces excitation of thyroid. With suppression of the suprarenals the iodine of the thyroid rapidly diminishes. On the other hand, feeding with suprarenals (whole gland)

¹ *Verhandl. d. 24. Kongr. f. inn. Med.*, 1907.

² A. M. Pappenheimer, *Proc. soc. exper. biol.*, xi, 1912.

³ Ross and Davis, *Journ. Pharm. and Exper. Therap.*, xx., 1922.

⁴ *Arch. intern. Med.*, xiii., 1914.

⁵ *Ibid.*, xix., 1917.

⁶ This subject has already been partly considered in treating of the thyroid.

⁷ *Arch. internat. de Physiologie*, xiv., 1914.

⁸ *Ibid.*, xiv., 1913.

⁹ *Amer. Journ. Physiol.*, lix., 1922.

causes a considerable increase in the iodine of the thyroid.¹ No effect was got with adrenaline, and the result is presumably due to cortex. G. A. Friedman,² on the other hand, looks upon hyperfunction of the medulla associated with hypofunction of the cortex as promoting activity of the thyroid and causing exophthalmic goitre, whilst the opposite conditions of the cortex and medulla produce symptoms of myxoedema. This view seems, however, incompatible with the fact that adrenaline causes improvement in some cases of exophthalmic goitre.³

Herring found that the administration of fresh ox-thyroid daily (0.2 to 0.5 gram), to white rats increases the size and weight of the suprarenals. Thus he obtained in 18 male animals, fed for 3 to 4 weeks, an increase of weight of 79 per cent. above the normal. Both cortex and medulla participated in the enlargement, but the cortex more than the medulla. In cats, as already pointed out (p. 63), the absolute amount of adrenaline contained in the glands is increased by thyroid feeding, and this is also the case with the white rat, although owing to the relatively greater increase in size of the cortex, the percentage for the whole gland is decreased. It appears probable that the increase affects also the accessory suprarenals; these are more easily discovered after thyroid feeding than in the normal animal.⁴ In confirmation of E. R. Hoskins, Herring found that the reaction of the suprarenals to thyroid is relatively greater in male than in female rats.⁵

A. T. Cameron⁶ has confirmed most of these results both with thyroid and thyroxin feeding, but the thyroxin effect is from 25 to 50 per cent. less than that of thyroid, compared on iodine content. When thyroid and suprarenal cortex are fed together in the proportion of 1 to 10-20 they antagonize one another.

¹ Black, Hupper, and Rogers, *Amer. Journ. Physiol.*, lix., 1922.

² *Med. Rec.*, Feb. 19, 1921. See also H. Swiecicki, *Presse méd.*, 1921.

³ Shapiro and Marine got amelioration of a case of exophthalmic goitre from administration of the whole gland, but a more marked effect when cortex alone was given, *Endocrinology*, v., 1921.

⁴ P. T. Herring, *Quart. Journ. Exper. Physiol.*, xi., 1917.

⁵ *Ibid.*, p. 236, and xii., 1919. Also in *Endocrinology*, iv., 1920.

⁶ Proc. XIth Internat. Physiol. Congress, *Quart. Journ. Exp. Physiol., Suppl. Vol.*, 1923.

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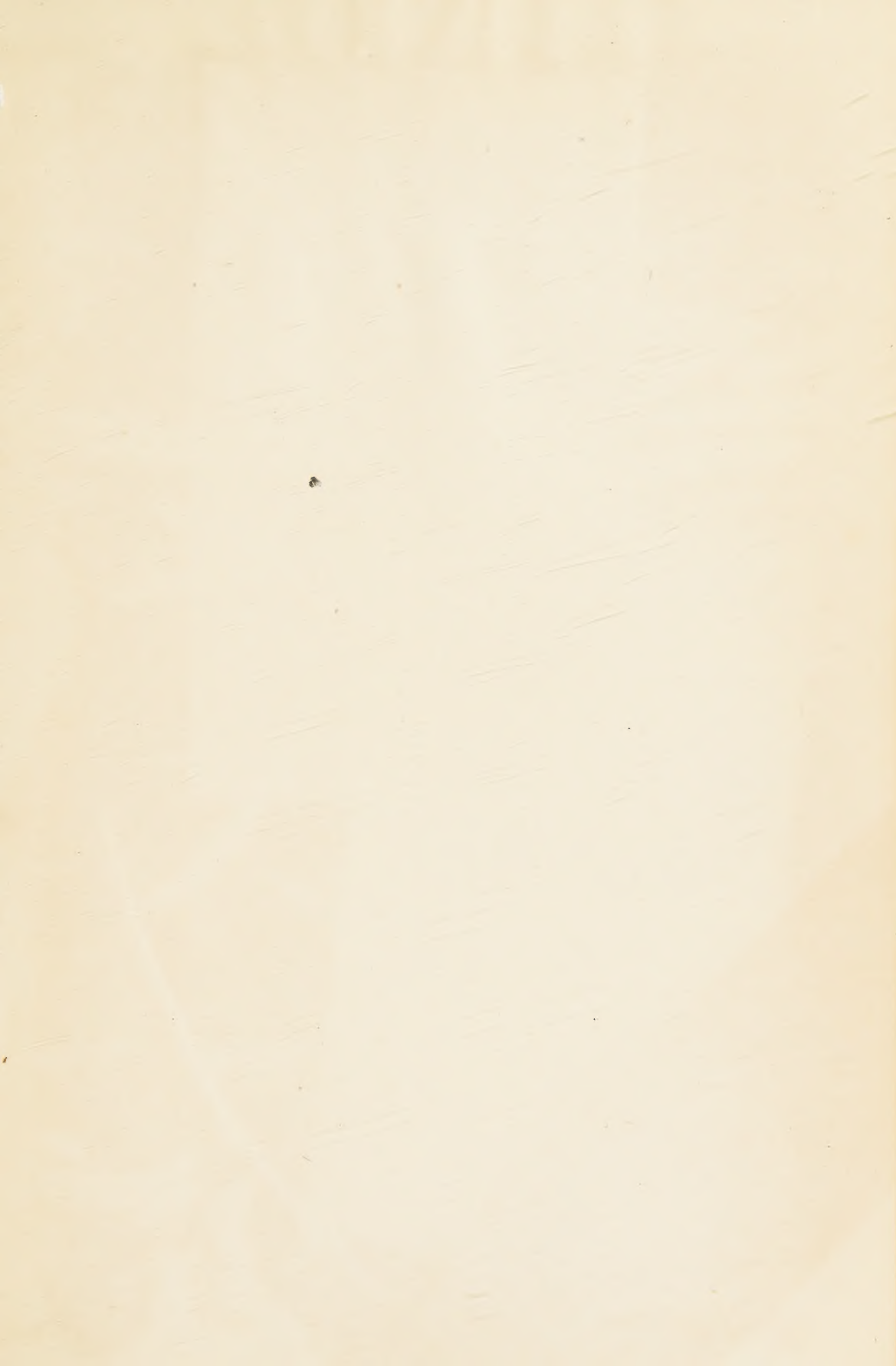
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